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# The Relationships Among Emotion, Cognitive Dysfunction and Anosognosia in Huntington's Disease

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The Relationships Among Emotion, Cognitive Dysfunction and  
Anosognosia in Huntington's Disease

by

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A dissertation submitted in partial fulfillment  
of the requirements for the degree of  
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## TABLE OF CONTENTS

List of Tables	v
List of Figures	vii
Abstract	ix
Chapter One: Introduction	1
Huntington’s Disease	1
Metacognition and Anosognosia	3
Models of Anosognosia	4
Hierarchical Models	4
Dynamic Model	6
Cognitive Awareness Model (CAM)	7
Toglia and Kirk’s Model (2000)	8
Anatomical Correlates of Awareness	10
Measuring Anosognosia	12
Self-Report and Interviewing Methods	13
Performance Prediction and Evaluation Method	14
Anosognosia Studies in Huntington’s disease	15
Metacognitive Knowledge of Behaviors	15
Online Awareness	17
Anosognosia in Other Neurodegenerative Populations	18
Alzheimer’s Disease (AD)	18
Parkinson’s Disease (PD)	20
Frontotemporal Dementia (FTD)	20
Summary of Anosognosia in Neurodegenerative Disorders	22
Rationale of the Current Study	22
Clinical Implications of Anosognosia in HD	22
Examining the Relationship Among Anosognosia and Cognitive and Mood Factors	23
Executive Functioning	23
Emotion	24
Memory	25
Rationale for Methods	26
Using Discrepancy Scores to Measure Metacognitive Awareness	26
Using Performance Prediction and Evaluation to Measure Online Awareness	26
Purpose of the Current Study	28

Main Hypotheses	28
Hypothesis One - Metacognitive Knowledge	28
Hypothesis Two - Anticipatory Awareness	28
Hypothesis Three - Emergent Awareness	29
Chapter Two: Methods	31
Participants	31
Participant Characteristics – Huntington’s Disease Patients	31
Participant Inclusion Criteria	32
Participant Exclusion Criteria	32
Participant Characteristics – Informants	33
Informant Inclusion/Exclusion Criteria	35
Participant Recruitment	35
Measures	37
Self-Report Measures	37
Clinician Administered Measures	38
Huntington’s Disease Diagnostic and Neurologic Measures	39
Cognitive Measures	40
Screening Measure	40
Executive Functioning Tasks	40
Memory Task	42
Anticipatory and Emergent Awareness Tasks	42
Procedures	44
Patients Recruited from the Neurology Clinic or HD	
Research Registry	44
Participants Who Also Participated in Enroll-HD	45
Study Procedures for All Participants	45
Patient procedures	45
Informant procedures	46
Confidentiality procedures	46
Chapter Three: Results	47
Hypothesis One - Metacognitive Knowledge	47
Main Proposed Analysis for Hypothesis One	47
Examination of assumptions for regression for Hypothesis One	49
Hypothesis One: Metacognitive Knowledge regression results	50
Exploratory Analyses of Metacognitive Knowledge	53
Exploratory analysis: Comparing patient and	
informant ratings (49 participants)	54
Apathy	55
Executive Dysfunction	55
Memory	56
Exploratory analysis: Examining patient and	
informant agreement based on overall	
cognitive impairment using the MoCA	58

Exploratory analysis of Metacognitive Knowledge: Associations between cognitive performance and self-report ratings (49 participants)	60
Hypothesis Two - Anticipatory Awareness	61
Validity Check for Performance Prediction (Anticipatory Awareness) and Evaluation (Emergent Awareness) Rating Method	62
Main Proposed Analysis for Hypothesis Two	63
Regression assumptions and diagnostics	63
Anticipatory Awareness: Regression results (51 participants)	64
Hypothesis Three - Emergent Awareness	66
Main Proposed Analyses of Hypothesis Three	67
Regression assumptions and diagnostics	67
Emergent Awareness/Performance Evaluation: Regression results	69
Exploratory Analyses for Online Awareness	70
Exploratory analysis: Relationships between patient ratings and actual performance	70
Exploratory analysis: Differences between Prediction ratings (Anticipatory Awareness), Evaluation ratings (Emergent Awareness) and actual performance	70
NAB Judgment	73
NAB Driving	74
NAB Immediate Memory Medications	74
NAB Delay Memory Medications	75
NAB Recognition Memory Medications	75
NAB Immediate Memory Address	76
NAB Delay Memory Address	77
NAB Recognition Memory Address	77
Exploratory Analysis: Metacognitive Knowledge and Online Awareness	77
Chapter Four: Discussion	79
Metacognitive Knowledge in HD	79
Is Metacognitive Knowledge Domain Specific?	80
Patient and Informant Report Compared with Objective Cognitive Measures	83
Metacognitive Knowledge and Caregiver Burden, Demographic Characteristics, and Disease Progression	86
Caregiver Burden	86
Gender	86
Age	87
Education	87
Motor Scores	87
Metacognitive Knowledge Conclusions	87
Online Awareness	88
Is Online Awareness Domain Specific?	89

Online Awareness and Relationships with Disease Progression and Demographic Characteristics	92
Motor Scores	92
Education	92
Age	92
Online Awareness Conclusions	92
Psychological Explanations for the Results	93
Study Limitations and Future Directions	94
Relationships between Metacognitive Knowledge and Online Awareness	94
Addressing Denial versus Anosognosia	95
Use of a Comparison Group	95
Control Group	95
Alzheimer’s Disease	96
Additional Factors	96
Methods Limitations	97
Statistical Power	97
Patient Past Exposure to Neuropsychological Testing	97
The AES-C	97
EMQ-R	98
Executive Functioning Tests	99
Conclusions	99
Chapter Five: References	101
Appendix A: Procedure Information	123
Appendix B: Informant Demographics Questionnaire	125
Appendix C: Descriptive Statistics	126
Appendix D: General Data Diagnostics	130
Appendix E: Additional Analyses for Metacognitive Knowledge	133
Appendix F: Additional Analyses for Anticipatory Awareness	142
Appendix G: Additional Analyses for Emergent Awareness	145
Appendix H: Institutional Review Board Approvals	147

## LIST OF TABLES

Table 1:	Comparison between patient and informant demographic information	34
Table 2:	Relationship Quality Based on Informant Report	34
Table 3:	Patient Recruitment Information for Final Sample	35
Table 4:	Metacognitive Analysis with motor scores (48 participants)	51
Table 5:	Apathy ratings for groups based on MoCA scores	58
Table 6:	The Relationship Between Patient and Informant Reports and Neuropsychological Test Results	61
Table 7:	Kendall's Tau Correlations: Verbal statement of ratings and percentile ratings using the bell curve method	62
Table 8:	Multivariate Multiple Regression for Memory and Executive Anticipatory Awareness (Performance Predictions)	65
Table 9:	Multivariate Multiple Regression Analysis: Emergent Awareness (45 Participants)	68
Table 10:	Relationship between performance prediction (Anticipatory Awareness) and evaluation (Emergent Awareness) percentile ratings and actual performance	71
Table 1A:	Order of counterbalanced neuropsychological tasks	124
Table 2A:	Patient Disease Characteristics: Main Variables of interest are bolded and have skewness and kurtosis listed	126
Table 3A:	Descriptive Statistics of Predictor Variables Neuropsychological Measures & Apathy for the Sample	127
Table 4A:	Descriptive Statistics of Main Variables – Metacognitive Knowledge Variables	128

Table 5A:	Descriptive Statistics of Main Variables – Performance Prediction Evaluation Variables	129
Table 6A:	Normative data available for each measure	131
Table 7A:	Correlations between main predictors and outcome variables for Metacognitive Knowledge	134
Table 8A:	Relationships between Metacognitive Knowledge and Memory	136
Table 9A:	Correlations between Executive Measures and Metacognitive Knowledge	137
Table 10A:	Relationships among Metacognitive Knowledge variables and control variables	138
Table 11A:	Metacognitive Knowledge Model without Motor Scores	138
Table 12A:	Metacognitive Analysis without Motor Scores (48 participants)	140
Table 13A:	Correlations between main predictors and outcome variables for Anticipatory Awareness	144
Table 14A:	Correlations between main predictors and outcome variables for Emergent Awareness	146



## LIST OF FIGURES

Figure 1:	Hypothesis One	29
Figure 2:	Hypothesis Two	30
Figure 3:	Hypothesis Three	30
Figure 4:	Recruitment Flow-chart	36
Figure 5:	Multivariate Multiple Regression Results	52
Figure 6:	Mean informant and patient ratings of Apathy based on informant rating tertiles	56
Figure 7:	Mean informant and patient ratings of Executive Dysfunction based on informant rating tertiles	57
Figure 8:	Mean informant and patient ratings of Memory based on Informant rating tertiles	57
Figure 9:	Informant and patient ratings of Apathy based on patient performance on the MoCA	59
Figure 10:	Informant and patient ratings of Executive Dysfunction based on patient performance on the MoCA	59
Figure 11:	Informant and patient ratings of Memory based on patient performance on the MoCA	60
Figure 12:	Model for Multivariate Multiple Regression Analysis: Anticipatory Awareness/Performance Prediction	66
Figure 13:	Model for Multivariate Multiple Regression Analysis: Emergent Awareness/ Performance Evaluation	69

Figure 14:	Performance Prediction and Evaluation Ratings and Actual Performance	72
Figure 15:	Patient ratings of Judgment and actual performance by tertile group based on actual performance	73
Figure 16:	Patient ratings of Driving and actual performance by tertile group based on actual performance	75
Figure 17:	Patient ratings of Immediate Memory for Address and actual performance by tertile group based on actual performance	76
Figure 18:	Patient ratings of Recognition Memory for Address and actual performance by tertile group based on actual performance	78
Figure 1A:	Relationship between Metacognitive Knowledge of Apathy and Unstructured Task Performance	134
Figure 2A:	Relationship between Metacognitive Knowledge of Apathy and Stroop Interference Scores	135
Figure 3A:	Relationship Metacognitive Knowledge of Executive Functioning and Stroop Interference	135
Figure 4A:	Multivariate Multiple Regression Results (no motor scores included)	141

## ABSTRACT

Huntington's disease (HD) is a genetic, neurodegenerative disorder that is characterized by motor, cognitive and psychiatric disturbances. Anosognosia, or lack of awareness of symptoms, is commonly observed in neurodegenerative disorders, including HD. Most theories suggest that emotion, executive functioning, and memory play important roles in self-awareness. There is limited research of anosognosia in HD and no theoretical model of how it manifests in the disease. The purpose of this study was to examine *Metacognitive Knowledge*, or overall beliefs about the self, and *Online Awareness*, or the ability to predict (Anticipatory Awareness) and evaluate (Emergent Awareness) task performance, in HD. Fifty-six symptomatic HD patients and fifty informants completed the study. Results revealed that those with the best executive functioning and lowest apathy were also better able to report on their symptoms. Those with the best executive functioning and memory and lowest apathy were the best at predicting and evaluating their performance on cognitive tasks. Patient self-report of memory was associated with cognitive performance while self-report of executive functioning and apathy was not. Only informant report of apathy and executive functioning was related to cognitive performance. For both Metacognitive Knowledge and Online Awareness, HD patients tended to have a better awareness of memory than executive functioning. These results suggest that awareness in HD is governed by local monitoring systems rather than a single metacognitive mechanism. It is also consistent with literature that suggests that individuals are least able to

evaluate performance on tasks for which they are poorest in skill level, as HD patients tend to have impaired executive functioning and increased apathy with relative sparing of memory.

## **CHAPTER ONE: INTRODUCTION**

### **Huntington's Disease**

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease that is characterized by motor, cognitive, affective, and behavioral disturbances (Novak & Tabrizi, 2010). The incidence rate of the disease has been estimated to be 0.38 per 100,000 per year, with lower incidence rates in Asia compared to Europe, North America, and Australia. Worldwide prevalence has been estimated at 2.71 per 100,000 (Pringsheim et al., 2012). HD is caused by an abnormal cytosine-adenine-guanine (CAG) trinucleotide repeat expansion of the huntingtin gene on chromosome 4 resulting in the production of abnormal huntingtin protein. The function of this protein in healthy individuals is unknown (MacDonald et al., 1993; Paulsen, 2011; Walker, 2007). Individuals who have a CAG repeat length of 39 or more are considered to be gene positive and will develop Huntington's disease during a normal human lifespan (Walker, 2007). While evidence suggests that CAG repeat length may influence when motor symptoms manifest, repeat length is often not associated with the nature of disease progression within individuals (Kiebertz et al., 1994; Lee et al., 2012; Rosenblatt et al., 2012). Currently, HD is diagnosed when there is either a positive genetic test or a family history of HD in addition to unequivocal extrapyramidal motor signs (Paulsen, 2011). Patients who have tested positive for the CAG repeat expansion but have yet to develop motor symptoms are considered to be in the prodromal stage of the disease (Pringsheim et al., 2012). Current classifications of disease onset do not take

into account that psychiatric and behavioral disturbance and cognitive impairment are often observed long before motor symptoms are expressed (Bonelli & Cummings, 2008; Duff, Paulsen, Beglinger, Langbehn, & Stout, 2007; Paulsen, 2011; Thompson, Snowden, Craufurd, & Neary, 2002). Both cognitive and emotional symptoms have been found to be associated with functional capacity independent of motor symptoms, disease duration, and demographic information (Nehl, Paulsen, & Huntington Study Group, 2004).

Often classified as a subcortical neurodegenerative disease, HD pathology results in reduced gray matter volume, beginning in the striatum (i.e. putamen and caudate) followed by the cerebral cortex (Novak & Tabrizi, 2010; Tabrizi et al., 2009). Striatal volume is reduced as many as twenty years prior to the onset of motor symptoms (Aylward et al., 2004). Reduced striatal volume impacts frontal-subcortical circuits, which connect subcortical regions to the limbic system and frontal lobes (Bonelli & Cummings, 2008). When these circuits are disrupted, symptoms associated with damage to the prefrontal cortex, such as executive dysfunction and apathy, are commonly observed (Unschuld et al., 2013; Van Duijn, Reedeker, Giltay, Roos, & Van der Mast, 2010). This has been demonstrated in a study that suggested HD patients have decreased connectivity between the anterior cingulate cortex and lateral prefrontal cortex when performing tasks of inhibition (Thiruvady et al., 2007). Furthermore, in early stages of the disease, cerebral white matter volume is also reduced, which is associated with poorer performance on tasks of processing speed and inhibition (Beglinger et al., 2005).

Studies have also suggested that anosognosia, or unawareness of deficits, may develop with the progression of HD. Patients have been shown to have decreased awareness of several domains, including executive functioning, behavioral and emotional control, and activities of daily living (Chatterjee, Anderson, Moskowitz, Hauser, & Marder, 2005; Ho, Robbins, &

Barker, 2006; Hoth et al., 2007). While several studies have examined anosognosia in HD, mechanisms that are associated with anosognosia in HD are still unknown. Though no imaging studies have been conducted to date, observed unawareness may be due to disruptions in frontal-subcortical circuits (McCusker & Loy, 2014; Sitek, Thompson, Craufurd, & Snowden, 2014). It is important to gain a better understanding of anosognosia in this population because unawareness may have a significant impact on patient care and safety (McCusker & Loy, 2014).

### **Metacognition and Anosognosia**

Anosognosia is a multifaceted construct that refers to a lack of awareness or recognition of illness or deficits. Babinski was the first to introduce the term “anosognosia,” referring to a lack of awareness of motor deficits observed in patients with hemiplegia (Prigatano, 2010). Anosognosia can impact some functional domains and not others and manifests in neurologic disorders, including HD (Jenkinson & Fotopoulou, 2014; Landes, Sperry, Strauss, & Geldmacher, 2001; McCusker & Loy, 2014; Nurmi & Jehkonen, 2014; Prigatano, 2010; Sitek et al., 2014).

Models of general self-awareness suggest that the construct of *the self* is supported by different brain functions and processes and different knowledge bases (Boyer, Robbins, & Jack, 2005). Gallagher distinguished between the *minimal self*, which involves the sense of ownership of one’s own body and the *narrative self*, which involves social identity, autobiographical memory, and continuity over time. He also described the concept of agency as being the sense of ownership of one’s actions or thoughts and the understanding that the self is the one undergoing an experience (Gallagher, 2000). Some suggest that autobiographical memory, comprised of episodic memory and semantic information about one’s own past is essential in the development

of one's sense of self. Memory allows for the ability to compare current experiences to past experiences and to support the idea that *the self* is durable over time and separate from other individuals (Boyer et al., 2005; Conway, 2005; Morris & Mograbi, 2013). Additionally, theory of mind and empathy appear to be important for supporting the idea that the self is distinct from other individuals (Boyer et al., 2005).

### **Models of Anosognosia**

Theoretical models of anosognosia provide a framework for asking questions and providing a basis for determining methods of measurement to enhance construct validity of studies (Jenkinson & Fotopoulou, 2014; Prigatano & Johnson, 2003). One of the challenges in studying anosognosia is that there is currently no theoretical model of anosognosia that is universally accepted (Prigatano, 2010). Some of the more studied models are described below.

#### **Hierarchical Models**

Stuss and Alexander (2000) postulate a hierarchical model of awareness that includes four levels of awareness in the following order: arousal-attention, perceptual-motor, executive mediation, and self-awareness. There are bidirectional relationships between each level. The two highest levels, executive mediation, and self-awareness are associated with prefrontal cortex functioning. They argue that the highest level of the hierarchy, self-awareness, is the result of the convergence of mood states and memory of abstract states, which allows for expectancy for the future.

Similarly, The Prigatano and Johnson (2003) model suggests that there are three vectors of consciousness that are arranged in a hierarchical manner: 1) wakefulness, 2) the sense of being



aware of the self, and 3) theory of mind. They suggested that the three vectors interact, involve overlapping neural circuits, and evolve over time to allow for the survival of the person. Additionally, they suggest that heteromodal cortex is important for the development of vectors two and three. Heteromodal cortex refers to brain regions that receive input from multiple sensory or multimodal areas and allow for the integration of information from multiple sensory modalities. Heteromodal cortex is associated with higher order levels of functioning because of integration of several cognitive functions (Blumenfeld, 2002; Donnelly, 2011). Many studies across patient populations support the theory that there is a relationship between the heteromodal cortex (i.e. prefrontal lobe, inferior parietal lobe, angular gyrus, supramarginal gyrus, and the anterior tips of the temporal lobe), unawareness, and theory of mind (Adenzato, Cavallo, & Enrici, 2010; Decety & Sommerville, 2003; Keenan, Nelson, O'Connor, & Pascual-Leone, 2001; Keenan, Wheeler, Gallup, & Pascual-Leone, 2000; Rosen, 2011; Toglia & Kirk, 2000).

Clare and colleagues recently proposed another hierarchical model of awareness. From lowest to highest, the levels of awareness include sensory registration, performance monitoring, evaluative judgment, and meta-representation. Similar to the Stuss and Alexander (2000), this model suggests that performance monitoring may also be influenced by beliefs and expectations, task knowledge, feedback, and emotion. Evaluative judgment reflects the general awareness of abilities, such as understanding one's own overall memory functioning or driving ability. They suggested that evaluative judgment is separate from performance monitoring in that a patient may be able to identify task-specific errors but may still maintain he or she has no difficulty in that cognitive domain, such as memory. Similar to Prigatano and Johnson's (2003) concept of theory of mind, meta-representation involves self-reflection and the ability to consider others' perspectives. This includes being aware of having a specific diagnosis and awareness of the

impact of symptoms on his or herself (e.g. everyday activities) or others. The individual's knowledge and experience, emotions and attitudes, cultural perspectives, and self-reflection influence meta-representation (Clare, Marková, Roth, & Morris, 2011).

### **Dynamic Model**

Rosen (2011) suggested that awareness is not necessarily hierarchical and that each success or failure in task performance leads to changes in self-appraisal. Like many of the other models, this theory argues the importance of considering memory and executive functioning in a model of unawareness, as both are important in self-appraisal. When a person completes a task, there is an activation of performance monitoring systems that compare performance with task demands. When a discrepancy is detected, emotional modulators mark the event with a level of importance and allow for the event to be evaluated. This information is then stored in long-term memory and may be used to update beliefs of one's own abilities. Rosen emphasized the importance of the emotional component of his model. He suggested that motivation may impact the level of monitoring and may also enhance monitoring through the impact of failed tasks.

Overall, most models of awareness are in agreement that several brain processes and regions are involved in the development of self-awareness. Hierarchical models of awareness suggest that lower cognitive functions feed into higher cognitive functions to develop awareness. In dynamic models, different processes interact to develop awareness. In both hierarchical and dynamic models, executive functioning, emotion, and memory are suggested to be important processes involved in awareness. Another model called the Cognitive Awareness Model (CAM) provides an in-depth framework for understanding how these processes interact to influence self-awareness in neurodegenerative diseases. This model is described in detail below. Also described

below in detail, is the Toglia and Kirk Model (2000), as it provides a framework for examining general awareness and awareness within the context of a task. Taken together, these two models may help provide guidance to better our understanding of anosognosia in HD.

### **Cognitive Awareness Model (CAM)**

Like other models, the CAM model also acknowledges that anosognosia is multifaceted and can result from different lesions of the brain (Agnew & Morris, 1998; Hannesdottir & Morris, 2007; Mograbi & Morris, 2014; Morris & Mograbi, 2013). This model originated from Schacter's Dissociable Interactions and Conscious Experience Model (DICE) in which he proposed an overarching mechanism of conscious awareness that interacts with other cognitive systems, such as memory (FitzGerald, Carton, O'Keefe, Coen, & Dockree, 2012; Schacter, 1990). Agnew and Morris (1998) extended the DICE model to explain anosognosia in dementia populations. The model suggested that unawareness occurs when there is a failure to update semantic memory about the self in the "Conscious Awareness Mechanism." A core component of awareness is the Personal Database (PDB), which consists of semantic representations of conceptual knowledge, including information about one's own abilities. The PDB changes over the lifetime and is influenced by activities and personal experiences. The PDB serves as a reference to make evaluative judgments of the self. The model also identifies a central Cognitive Comparator Mechanism (CCM) that is under executive control. The purpose of the CCM is to compare incoming information to the PDB. If there is a discrepancy, information is sent to the Metacognitive Awareness System, which brings the failure to conscious awareness. Issues with the CCM may lead to non-domain specific anosognosia. Unawareness may be due to a failure to encode information ("mnemonic anosognosia") or a failure to recognize a mismatch between

previously known information about the self and new incoming information because of a problem with the comparator mechanism (“executive anosognosia”). This suggests that executive dysfunction and memory may have separate contributions to awareness. For example, a study demonstrated that unawareness was associated with executive functioning but not memory performance in cerebral small vessel disease patients. Unawareness was associated with memory functioning in AD, however, and the relationship between executive functioning and awareness was only trending (Brookes, Hannesdottir, Markus, & Morris, 2013). The model also incorporates the impact of motivation and emotion. The theory suggests that when apathy is present, the lack of emotion or motivation results in the failure of stimuli and events to receive attention. This leads to reduced error monitoring and as a result, errors and consequences are ignored. Additionally, depression may lead to more awareness because it may lead to negative biases when judging self-ability, which may impact biased recall of negative information (Mograbi & Morris, 2014; Morris & Mograbi, 2013).

### **Toglia and Kirk’s Model (2000)**

Toglia and Kirk’s model was developed as a modification of Crosson and colleague’s (1989) Pyramid Model. This model purports that awareness is not a unitary construct, as supported by neuroanatomical studies that show multiple areas and neural pathways that are associated with awareness (Crosson et al., 1989; Toglia & Kirk, 2000). Toglia and Kirk’s model suggests that there are two types of awareness: metacognitive knowledge and online awareness. Metacognitive Knowledge (also called intellectual knowledge) is the overall knowledge and beliefs about the self or one’s own impairments. Metacognitive Knowledge exists outside of engagement in a task or situation. Online Awareness is activated within tasks and situations.

There are two types of Online Awareness. Online anticipatory awareness is the ability to predict problems before they occur as a result of a deficit. Online emergent awareness is the ability to monitor performance and to recognize errors while they occur. Both Metacognitive Knowledge and emergent awareness are necessary for anticipatory awareness because pre-existing knowledge and self-awareness interact within the context of the task. Some suggest that anticipatory and emergent awareness may be related to each other and separate from metacognitive awareness (O'Keeffe, Murray, et al., 2007; Rosen et al., 2014). Similar to the other models of awareness, affective states are thought to influence expectations of performance. Other factors that contribute to unawareness include issues with self-knowledge, overestimation of task performance prior to task performance and task performance itself. Other contributing factors of unawareness that have similarly been identified in other models include the ability to self-monitor, the inability to adjust performance, difficulty with self-evaluation, and the inability to integrate new experiences over time. A weakness of this model is that it does not identify specific cognitive (e.g. memory, executive functioning) or emotional factors that may contribute to the development of metacognitive and online awareness. The model also distinguishes unawareness from denial, which is a psychological response to deficits rather than a true lack of recognition of deficits. They suggest that denial is a coping response that tends to be accompanied by blaming external sources, hostility, and anger, while true unawareness is accompanied by perplexity, surprise or indifference. They caution that unawareness and denial may occur simultaneously.

## **Anatomical Correlates of Awareness**

Several models of anosognosia have suggested that anosognosia is a multifaceted construct and therefore is associated with many different brain regions. In healthy individuals, there is evidence for a large-scale, supramodal network that mediates appraisal of self-relevant content regardless of content domain (Schmitz & Johnson, 2007). These large neural networks include prefrontal and temporal regions, the inferior parietal lobe, angular gyrus, and supramarginal gyrus. Activation is often more pronounced in the right hemisphere (Decety & Sommerville, 2003; Keenan et al., 2001; Keenan et al., 2000; Rosen, 2011; Toglia & Kirk, 2000). Additionally, the dorsorostral anterior cingulate cortex may be involved in the effortful regulation of attention to introspective information (Krueger 2009).

Accurate self-awareness involves encoding and retrieval of self-relevant information, a process that involves the medial prefrontal cortex (PFC) (Northoff et al., 2006; Schmitz & Johnson, 2007; Shany-Ur et al., 2014). Studies have shown that the medial PFC is most active when participants think about themselves, such as personality traits, mental states, and physical attributes, compared to when they think about others. This suggests that the medial PFC is involved in self-reflection processes (Jenkins & Mitchell, 2011). Conceptualizations of the actions of others are associated with the dorsal medial prefrontal cortex (DMPFC) while self-concept is associated with the ventral medial prefrontal cortex (VMPFC), though others who are more closely related to the person also activate ventral areas (D'Argembeau et al., 2007; Herbert, Herbert, & Pauli, 2011). Schmitz and Johnson (2007) suggested that two top-down networks are involved in self-appraisal. First, the ventral medial prefrontal cortex-subcortical network is involved with orienting to pre-attentive biasing information that is self-relevant. The dorsal medial prefrontal cortex-subcortical network is involved with introspection such as self-

reflection, evaluation, and recollection. Some have suggested that the dorsal medial PFC is related to more anticipatory inferences related to goal achievement while the VMPFC enables inference of emotional response and reward value following goal achievement (Krueger, Barbey, & Grafman, 2009). In addition to prefrontal regions, anterior regions of the temporal lobes are believed to play a role in storing knowledge and facts about the self and other individuals (Zahn et al., 2007; Zamboni et al., 2013).

Neuroanatomical findings in healthy populations are congruent with studies of awareness in neurodegenerative populations. In a study of neurodegenerative disease patients (i.e. Amyotrophic Lateral Sclerosis (ALS), mild cognitive impairment (MCI), Alzheimer's disease (AD), and Frontotemporal dementia), increased self-awareness was associated with greater right VMPFC activity and volume (Rosen et al., 2010). In a PET study of AD patients, impaired self-evaluation was associated with reduced activity in orbital prefrontal and medial temporal structures (Salmon et al., 2006). In an fMRI study, AD patients had to answer questions related to cognitive, behavioral and physical traits about themselves and their study partner. Activity was observed in the medial prefrontal cortex and anterior temporal lobes for MCI and control patients when rating both self and the informant, suggesting that these areas are associated with self-evaluation and also possibly evaluation of familiar individuals. For AD patients, however, the medial PFC was only activated during the other rating condition, not self-rating. Left anterior temporal lobe activation was decreased during the self-evaluation portion but increased during the other-evaluation condition. Larger discrepancies between self and caregiver report were associated with reduced activity in the medial prefrontal cortex and anterior temporal regions during the self-evaluation procedures. This suggests that the medial prefrontal cortex is involved with updated self-awareness (Zamboni et al., 2013).

The right hemisphere, in particular, has also been associated with self-awareness. Five right-handed patients undergoing the Wada test were shown pictures of faces that were created by morphing the patient's face with a famous person's face. Following recovery after anesthesia of each hemisphere, participants were presented with the two original unmorphed faces and were asked to choose which face they had seen previously. Following anesthesia of the left hemisphere, all patients selected their own face, while following right hemisphere anesthesia, four out of five patients selected the famous face. Similar results were found when they tested ten normal participants and used TMS to stimulate the right or left motor cortex (Keenan et al., 2001).

Anatomical substrates of anosognosia in symptomatic HD patients have yet to be studied, except one study of motor symptom anosognosia. A decrease in striatal volumes (i.e. left and right caudate and putamen) has been shown to be related to unawareness of motor symptoms in HD patients (Justo et al., 2013). McCusker and Loy (2014) suggested that given research in other neurodegenerative diseases and anosognosia, frontostriatal pathway disruptions are a likely contributor to impaired awareness in HD. McCusker and Loy (2014) also cited studies that have demonstrated increased denial of deficits following right basal ganglia infarcts, also supporting the idea that these pathways may be associated with increased unawareness.

### **Measuring Anosognosia**

Challenges exist in developing methods to study and operationalize anosognosia, which also creates challenges in comparing studies that use different methodology. Current methods include clinician ratings of patient unawareness, discrepancy scores between patient and informant report, discrepancies between patient report and task performance, or a combination of



the three methods (Clare, 2004; Nurmi & Jehkonen, 2014). Nurmi and Jehkonen (2014) indicated that many researchers only use one method in studies. In the future, perhaps using multiple methods within the same study can alleviate some of the challenges associated with measuring anosognosia by providing more information on the convergent validity of these methods.

### **Self-Report and Interviewing Methods**

Regarding discrepancies between patient and informant report, informants are theorized to be better able to give accurate ratings than patients. The use of questionnaires is advantageous in that they are easily administered, allow for the assessment of a wide range of functioning (e.g. activities of daily living, mood, cognitive functioning) and can be compared to different objective measures such as cognitive tests or neurologic motor exams. However, informant ratings are subjective, as other factors such as the caregiver's personality, quality of the relationship, and caregiver burden may influence informants' report (Clare, 2004; Hoth, 2005; Prigatano & Johnson, 2003; Toglia & Kirk, 2000). Clinicians may be more objective than caregivers and may be more familiar with the concept of unawareness and expectations of functioning in neurologic populations. However, clinicians rarely observe patients in real-world settings and typically obtain information from caregivers and patients, which may reduce objectivity of clinicians' rating (Clare, 2004; Hoth, 2005; Prigatano & Johnson, 2003). Some suggest patient/informant discrepancies are more valid for measuring awareness of everyday function, while clinician ratings may be more valid for measuring awareness of cognitive functioning, as studies have indicated that relationships between factors influencing awareness

are moderated based on measurement method used (Snow et al., 2005; Tremont & Alosco, 2011).

### **Performance Prediction and Evaluation Method**

The performance prediction and evaluation method involves the participant reporting on how well he or she will complete a task (prediction) or how well he or she has completed a task (evaluation). The outcome measure is quantifiable, as several research groups have come up with methods to measure performance prediction such as analog scales and bell curves. Convergent validity has been demonstrated for bell curve methods in dementia populations; high correlations (i.e. above  $r=.8$ ) have been found when comparing verbal prediction ratings and predictions using bell curve ratings (Williamson et al., 2009). Performance prediction and evaluation methods are considered the most objective measures of awareness because of the non-reliance on either a clinician or an informant. However, this method can only be used for tasks where performance can be measured by direct observation (e.g. a driving test) and cannot be used to measure other more inferred psychological constructs (e.g. depression). Furthermore, the ecological validity of this method must be considered. If a person had not been exposed to a similar task previously, it may be difficult for him or her to predict performance, regardless of how aware he or she is (Hoth, 2005; Williamson et al., 2009). Another consideration is performance prediction methods are not tapping into a pathological deficit, but rather a common feature of human cognition. For instance, Tversky and Kahneman (1974) suggested that heuristics, or mental shortcuts, may lead to errors in judgment. Specifically, availability heuristics influence the tendency of making decisions based on how easily past events come to mind. Confirmation biases is another heuristic that involves the tendency to seek out information

that confirms existing beliefs (Nickerson, 1998). If a person has a specific belief about his or her own cognitive abilities, they may discount information that does not match his or her beliefs. Even though heuristics may influence prediction and evaluation, it does appear that both healthy individuals and AD patients adjust their predictions after performing the same task several times (Ansell & Bucks, 2006).

## **Anosognosia Studies in Huntington's disease**

### **Metacognitive Knowledge of Behaviors**

Several studies have examined awareness of behavioral functioning in both prodromal and symptomatic HD patients. Most studies have used patient/informant discrepancy scores to determine unawareness of deficits in this population. In a study examining patient and informant agreement in prodromal HD patients, informants rated patients higher on all three subscales of the Frontal Systems Behavior Scale (FrSBe), which include Apathy, Disinhibition, and Executive Dysfunction when compared to gene negative at risk relatives. Both patient and informant report were related to motor symptoms as rated on a neurologic exam. However, only informant ratings were related to neuropsychological test performance. The authors also reported that when closer to HD diagnosis, prodromal patients showed greater discrepancies from informant ratings on FrSBe scales, which was interpreted as possible decreased awareness associated with disease progression. However, for those patients closest to predicted conversion to manifest HD, patient and informant ratings eventually became more consistent. The authors suggested that those in the earlier prodromal phase might be able to detect prefrontal dysfunction better than informants. As these symptoms become more pronounced, however, informants may

be better able to identify these symptoms (Duff et al., 2010). A continuation of this pattern using the FrSBe has been found in manifest patients. One study found no discrepancies between patient and informant report for those patients with less motor symptom progression, while informants tended to rate patients as more severe on the measure for patients with more severe motor symptoms. Additionally, only informant ratings of executive dysfunction and apathy were related to the severity of motor symptoms while patient ratings were not related (Hergert, Sanchez-Ramos, & Cimino, 2015). Another study that examined patient awareness in symptomatic HD patients found that when compared to informant ratings, patients overestimated their ratings of themselves in regards to behavioral and emotional control as well as their ability to manage activities of daily living. The most disagreement was found regarding emotional functioning. Furthermore, only informant ratings were associated with findings on the neurological exam. Interestingly, unawareness was associated with executive function and memory performance (Hoth et al., 2007).

Chatterjee et al. (2005) found that agreement between HD patient and informant report of neuropsychiatric symptoms, such as depression, apathy, and irritability, depended on the level of cognitive impairment present, with lower agreement observed when patients had worsening cognition. In a study examining awareness of dysexecutive behavior in HD, patients were found to more accurately rate their caregivers dysexecutive behaviors than their own dysexecutive behaviors, suggesting that HD patients are generally able to report on these behaviors in other people, but may have limited awareness of their own behaviors (Ho et al., 2006). In another study comparing anosognosia in HD and Parkinson's disease (PD), only informant report of dysexecutive behaviors was related to performance on tests of executive function for both HD patients and PD patients, though HD patients demonstrated more unawareness of executive

dysfunction than the PD patients (Sitek et al., 2013). Education has also been suggested to be associated with awareness in HD. One study showed that educated patients had an earlier age of onset, but had less severe symptoms. Authors have suggested more educated individuals may recognize symptoms earlier than those with less education (López-Sendón et al., 2011).

Two studies have examined awareness of memory deficits in HD. One study found that HD patients underestimate their memory functioning, as measured by patient-caregiver discrepancy scores, and that this underestimation of performance increases with disease progression as measured by the severity of motor symptoms. Both patient and informant report, however, were unrelated to memory performance on an objective memory measure (Sitek et al., 2012). Another study that measured awareness by correlating self-report and objective memory performance found that patients earlier in the disease process were more accurate at evaluating their own memory than informants, while informant ratings were more accurate for patients later in the disease process (de Langavant et al., 2013).

### **Online Awareness**

Online awareness is awareness of proficiency of performance before or after a task. Online awareness in HD has mainly focused on awareness of motor symptoms. In a study that used a videotaped interview to compare patient report to observed movements, anosognosia for chorea was observed in almost all participants. Controls were also interviewed in the same manner except the motor “symptoms” reported were normal involuntary movements such as twitches and postural changes. Results indicated that controls and prodromal HD patients were just as unaware of involuntary movements as early HD patients of their chorea, suggesting unawareness of movement observed in HD patients may not be pathological (Justo et al., 2013).

In another study of prodromal patients (PREDICT-HD data), 50% of patients who began to exhibit motor symptoms over the course of the study were unaware of their motor symptoms. Awareness was associated with increased depression (McCusker et al., 2013). HD patients have been shown to be less aware of involuntary movements than advanced PD patients (Sitek et al., 2011).

Limited research has been conducted examining metacognitive knowledge and online awareness in HD. Most studies suggest that awareness of cognition, behavioral and emotional functioning decreases as impairments in motor functioning and cognition increase. Furthermore, online awareness of motor symptoms has only been examined. Poorer self-awareness in HD may be related to a decline in orbitofrontal-limbic system functioning in HD, as HD patients may fail to attach a negative evaluation to impairments (Sitek et al., 2011).

## **Anosognosia in Other Neurodegenerative Populations**

### **Alzheimer's Disease (AD)**

Unawareness in Alzheimer's disease (AD) is nonspecific, as unawareness has been demonstrated across domains such as memory, executive functioning, language, and activities of daily living. Some have suggested that decline in memory abilities may be a contributor to unawareness in this population as patients are not able to remember new information about themselves (Mograbi, Brown, & Morris, 2009). In patients with probable AD, awareness of neurocognitive, behavioral and psychiatric disturbance predicted greater depressed mood and anxiety and less apathy while controlling for global cognition as measured by the Mini-Mental Status Exam (Horning, Melrose, & Sultzer, 2014). In a study examining the diagnostic

sensitivity of self and informant reports of cognition and cognitive testing in the prediction and detection of AD, informant report of current memory problems, changes in memory, and perceptions of the participant's cognitive abilities were found to predict diagnosis, while self-reports of the same information did not. This suggests that informants may be more accurate in describing patient behavior than AD patients themselves (Rabin et al., 2012).

In a study of online awareness of memory performance, AD patients and controls were given three different word lists that they would need to remember. Before each trial, participants were asked how many words they would remember. While AD patients had larger discrepancies between their predictions and actual words they recalled than controls, the results suggested that AD patients were able to revise their predictions based on past experiences. The authors suggested that perhaps in AD, the comparator mechanism, which is controlled by executive functioning, is somewhat preserved. This hypothesis is congruent with the idea that executive functioning is relatively preserved in AD compared to subcortical dementias (Ansell & Bucks, 2006). This is also supported by a more recent study that demonstrated AD patients were able to downgrade performance evaluation following a task when compared to their initial predictions, while frontotemporal dementia patients, a disease where executive dysfunction is more prominent, were less likely to downgrade performance (Williamson et al., 2009).

In a study of AD patients, unawareness of cognitive deficits was related to more apathy, cognitive impairment, and delusions, and less depression. Unawareness of behavioral deficits, however, was not related to cognitive impairment but was related to disinhibition and pathological laughter. Apathy was found to be the main correlate of anosognosia, suggesting that unawareness of deficits is more closely related to emotional changes than it is to cognitive impairment (Landes et al., 2001; Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996).

### **Parkinson's Disease (PD)**

Awareness in PD appears to be relatively preserved compared to other neurodegenerative populations as patients often report more impairments than informants. PD patients have been shown to report more executive dysfunction than healthy controls. Mild PD patients and caregivers had similar responses, indicating that patients have relatively good insight into their problems (Koerts et al., 2012). In another study, patient ratings indicated more impairment than informant ratings, except for apathy, which was the only area where patient and informant ratings were in agreement (McKinlay et al., 2008). Imaging studies in PD have suggested that in early PD, dopamine (DA) depletion is more severe in the putamen rather than the caudate. Furthermore, DA depletion is greatest in the rostradorsal portion of the caudate, which is associated with connections to the dorsolateral prefrontal cortex, areas associated with executive functions. Ventral regions of the caudate are connected to ventromedial portions of the prefrontal cortex, and functions of these areas, such as probabilistic learning, are often spared early in the disease (Cools, 2006; Cools, Barker, Sahakian, & Robbins, 2001; Leh, Petrides, & Strafella, 2010; Poletti & Bonuccelli, 2012). Perhaps awareness is relatively preserved in PD because the VMPFC is spared early in the disease.

### **Frontotemporal Dementia (FTD)**

FTD is another disorder in which anosognosia is frequently observed. In a study examining different metacognitive and online awareness among the behavioral variant of FTD, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) patients, metacognitive awareness was examined using a patient-caregiver discrepancy on the Patient Competency Rating Scale (PCRS), a measure specific to awareness and a clinician interview of



awareness. Anticipatory awareness was measured by performance prediction on cognitive testing. Emergent awareness was measured using a Go/No-Go task where the participant had to acknowledge every time they made an error by saying “hit.” FTD, CBD, and PSP are frequently associated with abnormal tau protein and are all associated with atrophy of the frontal and/or temporal lobes. All three patient groups were impaired across all three types of awareness described in the model. They found that the FTD group, however, showed greater online emergent awareness impairment than the CBD and PSP groups, which the authors suggested may be related to more severe prefrontal cortex damage that is more commonly found in FTD compared to the other disorders (O’Keeffe, Murray, et al., 2007). In another study, FTD patients showed greater behavioral unawareness than AD patients and healthy controls. FTD, AD, and control group performance prediction ratings were positively correlated to performance. When examining FTD subtypes, however, behavioral subtype (social dysexecutive) patients had difficulty predicting performance on a word memory task, while those with progressive non-fluent aphasia had difficulty predicting verbal association fluency performance (Eslinger et al., 2005). In a study examining awareness of cognition in AD and the behavioral variant of FTD patients, both groups showed an impaired feeling of knowing accuracy compared to controls and the severity of impairment was greater for the FTD group. Past research suggests a strong link between prefrontal cortex functioning and feeling of knowing ability. Additionally, FTD patients did not adjust performance predictions when provided feedback, which the authors noted is consistent with past findings that FTD patients are insensitive to negative feedback (Rosen et al., 2014). This supports the idea that anosognosia in FTD is related to a failure in online monitoring.

## **Summary of Anosognosia in Neurodegenerative Disorders**

In the neurologic patient populations described above, including HD, changes in awareness are associated with cognitive and emotional factors. When comparing patient groups, it appears that patients with more significant executive functioning (e.g. FTD) and memory (e.g. AD) impairments tend to demonstrate more severe symptoms of unawareness. In Parkinson's disease, awareness appears to be relatively spared, especially earlier in the disease progression, which may be due to the sparing of the VMPFC. Across disorders, patients with apathy tend to have higher rates of unawareness, suggesting a connection between awareness and emotional and motivational factors.

## **Rationale of the Current Study**

### **Clinical Implications of Anosognosia in HD**

Anosognosia is important to study in HD because it has several implications for the clinical care of patients as well as our understanding of anosognosia more generally. Studying unawareness of executive dysfunction may be particularly valuable, as behavioral executive function is associated with overall functioning in instrumental activities of daily living (IADLs)(Katzmark, Llanes, Tan, Deutsch, & Zeifert, 2012). Several studies have demonstrated that in different neurologic patient populations, anosognosia can impact the quality of life of the patient and caregiver (Rymer et al., 2002). For example, anosognosia in AD patients is related to less patient depression and reported better quality of life. However, it is also related to greater caregiver burden and greater discrepancies between patient and caregiver quality of life (Conde-Sala et al., 2013). In a study of TBI patients and their caregivers, caregiver distress was

significantly correlated with caregiver perception of patient unawareness (Prigatano, Borgaro, Baker, & Wethe, 2005). Additionally, anosognosia may inflict a financial burden on families for patients who need supervision because they are at risk for wandering or engaging in other risky behaviors such as driving (Rosen, 2011).

In HD specifically, unawareness can delay diagnosis and/or become a barrier to treatment (e.g. swallowing evaluations, obtaining proper walking aids). Unawareness may cause conflict within families between those who may be unaware and do not want to know their genetic status versus family members who do want to know their genetic status. Furthermore, for those who are still employed or still engaging in other instrumental activities of daily living such as driving, unawareness of certain cognitive and functional limitations may compromise the safety of the patient and others who may be impacted by the patient's actions. Additionally, it is important to understand who retains awareness, as those individuals are at increased risk for depression, anxiety, and suicide (McCusker & Loy, 2014).

### **Examining the Relationship Among Anosognosia and Cognitive and Mood Factors**

In most theoretical models, anosognosia is theorized to be a multifaceted construct that is associated with deficits in many brain regions and cognitive domains. Most models of anosognosia in the context of neurodegenerative diseases suggest that there are relationships between awareness and executive functioning, emotion, and memory (Clare et al., 2011; Mograbi & Morris, 2014; Rosen, 2011).

**Executive Functioning.** Executive functioning is an umbrella term that describes purposeful, goal-directed behavior (Banich, 2009) or mental operations that are needed in novel or in non-routine situations, in which there is not an established stimulus-response association

(Gilbert & Burgess, 2008). As described in several of the models above, executive functioning appears to be an essential component in self-monitoring, self-evaluating and the organization and retrieval of relevant autobiographical memories (Morris & Mograbi, 2013; Robertson, 2010). Due to executive functional impairments that often observed in both prodromal and symptomatic stages of the disease, it is likely that prefrontal dysfunction through degeneration of frontal-striatal pathways plays a role in anosognosia (McCusker & Loy, 2014; Sitek et al., 2014).

**Emotion.** Several models of awareness suggest emotional factors are important contributors to anosognosia because emotion impacts the salience of stimuli. The more salient the stimulus, the more likely one will remember it and refer to it later (Mograbi & Morris, 2014; Rosen, 2011; Stuss & Alexander, 2000). Anosognosia has been shown to be a predictor of severe apathy (Starkstein, Brockman, Bruce, & Petracca, 2010). Apathy has been defined as lack of motivation, which cannot be attributed to emotional distress, cognitive deficits, or loss of consciousness (Marin, 1991).

Apathy may be implicated in awareness in HD. Apathy is a common frontally mediated behavioral disturbance in HD, with studies reporting that between 32-50% of patients experience some degree of symptoms (Hamilton et al., 2003; Naarding & Janzing, 2003; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001; Van Duijn et al., 2010). The anterior cingulate cortex has been implicated in unawareness, error monitoring, and apathy (Beste, Saft, Andrich, Gold, & Falkenstein, 2006; Landes et al., 2001; Lavretsky, Ballmaier, Pham, Toga, & Kumar, 2007; Tekin & Cummings, 2002). This structure is impacted in HD through degeneration of projections from the striatum (Beste et al., 2006).

Preservation of awareness does seem to be a risk factor for developing depression. In AD, more depression is associated with less anosognosia (Mograbi & Morris, 2014; Starkstein et al.,

1996; Verhey, Rozendaal, Ponds, & Jolles, 1993). In schizophrenia, those with preserved awareness after the first psychotic episode are more likely to develop depression and commit suicide four years after the episode (Crumlish et al., 2005). According to the Beck model of depression, patients view themselves, their current situation, and their future situation negatively (Coyne & Gotlib, 1983). Some have suggested that depression is associated with less anosognosia due to a negative bias when reporting on problems related to symptoms. Another suggestion is that increased awareness of difficulties may lead to reactive depression, suggesting a protective role of anosognosia (Mograbi & Morris, 2014).

**Memory.** Finally, while memory appears to be an essential aspect of the development of the sense of self, it is unclear if changes in memory functioning significantly contribute to the development of anosognosia in HD. Some memory deficits are observed in HD but are often related to a decline in executive functioning as opposed to a true deficit in the ability to encode and retain memories. Memory retrieval is often impaired, but performance often improves when HD patients are provided information in a recognition format or when cued (Lezak, Howieson, Bigler, & Tranel, 2012). Hoth et al. (2007) reported that overall memory performance on the Dementia Rating Scale – 2 (DRS-2) was associated with unawareness in HD. It is unclear, however, which aspect of memory functioning may be contributing to unawareness and therefore a more comprehensive measure of memory is needed to examine how memory relates to unawareness in this population. Specifically, it remains unclear if there is an actual deficit in a specific aspect of memory (e.g. encoding, storage) that is associated with unawareness in HD, or if the memory problems are actually due to executive dysfunction resulting in a retrieval issue.

Studying how executive dysfunction, emotion/motivation, and memory are related to anosognosia can inform which factors most strongly contribute to unawareness in HD.

Additionally, this will allow for the examination of which model of anosognosia may best fit the pattern of unawareness observed in HD.

### **Rationale for Methods**

**Using Discrepancy Scores to Measure Metacognitive Awareness.** Informant or collateral report is one of several sources of information used in clinical decision-making for the HD population. Patient/informant discrepancy scores have been used to measure metacognitive knowledge, or one's overall knowledge of oneself or one's condition (O'Keefe, Dockree, Moloney, Carton, & Robertson, 2007; O'Keefe, Murray, et al., 2007; Toglia & Kirk, 2000). It has been suggested that discrepancy scores may be a suitable method to measure unawareness in HD. When HD patients report on another person's behavior, agreement between the patient and that person is high. However, when patients' ratings of their own functioning and behavior are compared to informant report, the discrepancies between the reports are larger, suggesting more disagreement. This suggests that discrepancies between patient and informant ratings may indicate a decrease in self-awareness (Ho et al., 2006; Hoth et al., 2007).

### **Using Performance Prediction and Evaluation to Measure Online Awareness.**

Measuring two types of anosognosia (i.e. Metacognitive Knowledge and Online Awareness) may provide more information about this multifaceted construct, as different factors (i.e. Executive Dysfunction, Apathy, and Memory) may be related to these types of awareness in a different fashion. A performance prediction and evaluation paradigm was included in the study to further examine HD patient awareness of performance on specific tasks. The performance prediction and evaluation technique is thought to allow for the measurement of Online Awareness from the Toglia and Kirk Model (Banks & Weintraub, 2008; O'Keefe, Dockree, et al., 2007; O'Keefe,

Murray, et al., 2007; Rosen et al., 2010; Toggia & Kirk, 2000). Specifically, *performance prediction* is thought to measure Anticipatory Awareness, while *performance evaluation* is thought to be a measure of error monitoring or Emergent Awareness (Banks & Weintraub, 2008). Several research groups have used performance prediction and evaluation methods with other neurodegenerative populations. This technique, however, has yet to be used in HD patients except for studies of motor awareness, which indicated that patients were unaware of their movements (Justo et al., 2013).

To obtain performance prediction and evaluation estimates, a method of asking participants to rate their performance on a bell curve was used. The bell curve method is advantageous over other performance prediction and evaluation methods because predictions, evaluations, and test scores will be on the same scale (i.e. percentiles) and are therefore more easily compared. The bell curve method has been used in performance prediction and evaluation studies in AD and FTD patients (Rosen et al., 2010; Williamson et al., 2009).

Some have suggested performance prediction may be more difficult for tasks that are not generally engaged during everyday functioning (Williamson et al., 2009). Because of the specific interest in examining Online Awareness of executive functioning and memory, participants predicted and evaluated their performance on the Everyday Functioning Executive Function and Memory subtests from the Neuropsychological Assessment Battery (NAB) The tasks were chosen as more ecologically valid measures of executive functioning and memory because the tasks were created to reflect tasks that may be encountered in everyday life (e.g. driving, remembering medication instructions). These tasks have been used in a performance prediction and evaluation study of Alzheimer's disease and frontotemporal dementia patients (Williamson et al., 2009).

## **Purpose of the Current Study**

The purpose of this study was to examine how cognitive (i.e. Executive Functioning and Memory) and emotional factors (i.e. Apathy) contribute to Metacognitive Knowledge and Online Awareness in symptomatic HD. *Metacognitive Awareness* of Executive Dysfunction, Memory, and Apathy and *Online Awareness* of Executive Dysfunction and Memory were examined.

## **Main Hypotheses**

### **Hypothesis One - Metacognitive Knowledge**

**(1)** *Cognitive Executive Functioning, clinician-rated Apathy, and cognitive Memory will be independently associated with Metacognitive Knowledge of Executive Functioning, Apathy, and Memory as measured by informant and patient discrepancies on self-report measures.* **(2)** *Executive Functioning and Memory will be positively associated with Metacognition Knowledge, while Apathy will have a negative association.* **(3)** *Apathy and Executive Dysfunction will be more strongly related to Metacognitive Knowledge than Memory.*

### **Hypothesis Two - Anticipatory Awareness**

**(1)** *Cognitive Executive Functioning, clinician-rated Apathy, and cognitive Memory will be independently associated with Anticipatory Awareness of Executive Functioning and Memory as measured by performance prediction on tasks of everyday functioning.* **(2)** *Executive Functioning and Memory will be positively associated with Anticipatory Awareness while Apathy will be negatively associated.* **(3)** *Apathy and Executive Dysfunction will have stronger relationships with Anticipatory Awareness than Memory.*



### Hypothesis Three - Emergent Awareness

(1) Cognitive Executive Functioning, clinician-rated Apathy, and cognitive Memory will be independently associated with Emergent Awareness of Executive Functioning and Memory as measured by performance evaluation on tasks of everyday functioning. (2) Executive Functioning and Memory will be positively associated with awareness while Apathy will be negatively associated. (3) Apathy and Executive Dysfunction will be greater contributing factors to Emergent Awareness in HD than Memory.

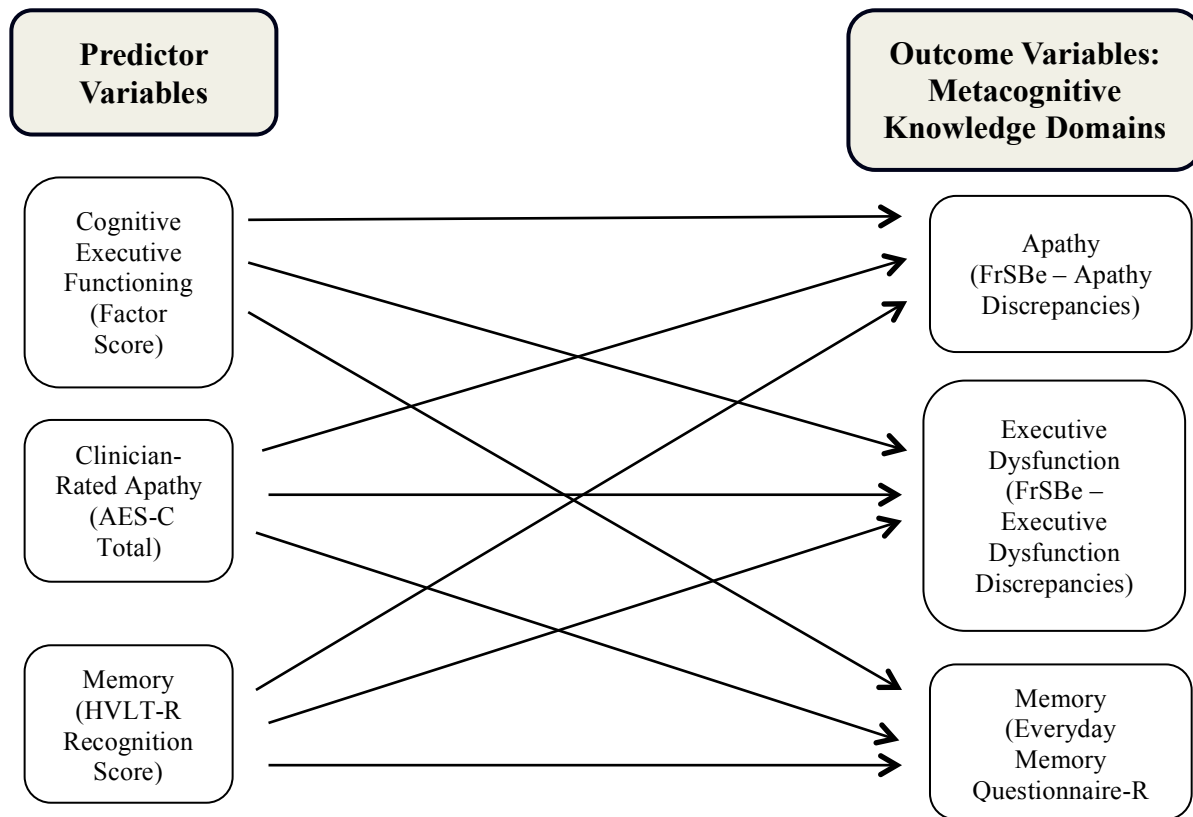
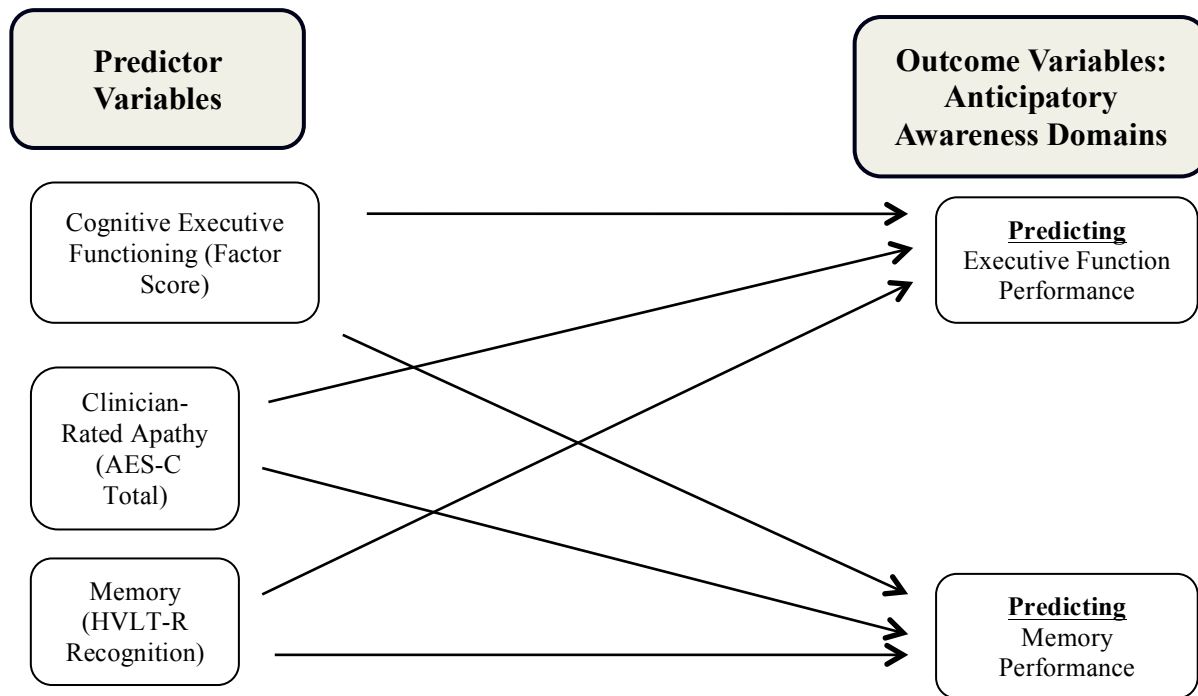
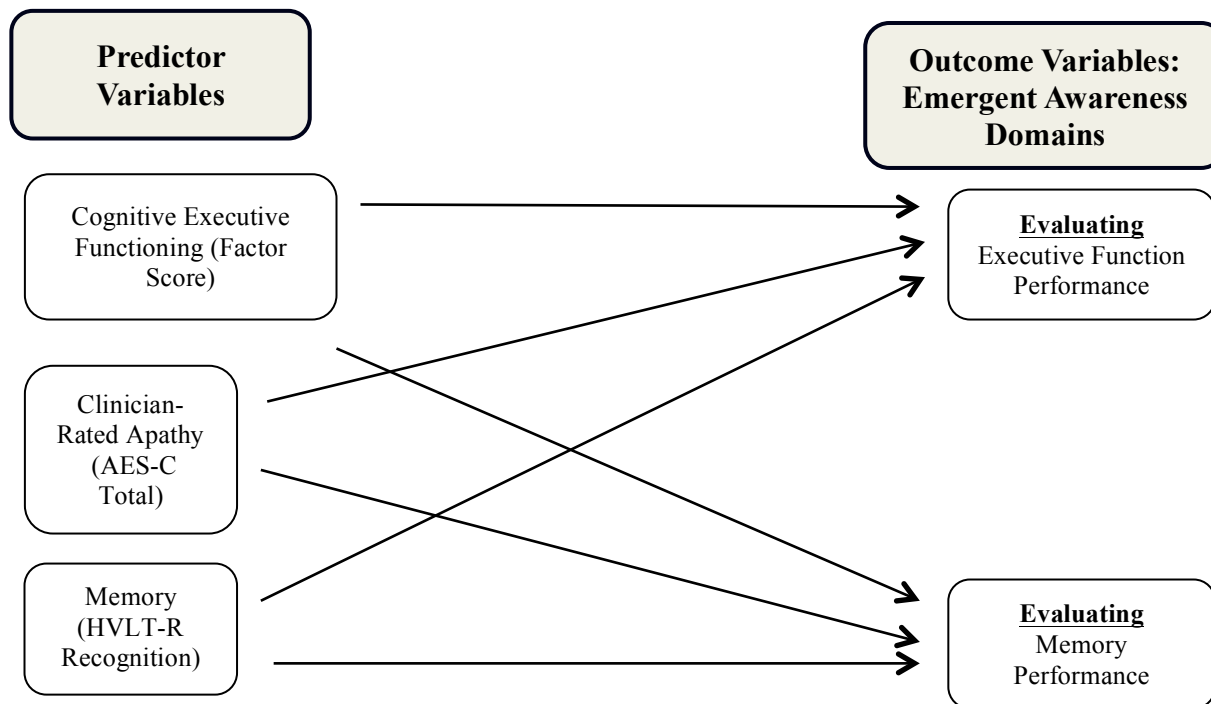


Figure 1. Hypothesis One.



**Figure 2.** Hypothesis Two.



**Figure 3.** Hypothesis Three.

## **CHAPTER TWO:**

### **METHODS**

#### **Participants**

Sixty-one patients with a diagnosis of Huntington's disease were recruited from the Huntington's Disease Society of America's (HDSA) Center of Excellence Clinic at the University of South Florida and signed informed consent. One additional patient was recruited but did not have the capacity to provide informed consent and was not enrolled in the study. Five participants who signed consent did not complete the study (one due to a history of head injury, three did not want to complete the cognitive testing, and one had difficulty understanding how to complete the self-report questionnaires). All five of these participants had informants who signed consent for the study and completed the informant questionnaires in person, but the informant data was not used in the final data analysis.

#### **Participant Characteristics – Huntington's Disease Patients**

Fifty-six Huntington's disease patients completed the study. In the final sample, there were 20 males (35.7%) and 36 females (64.3%), ages ranged from 33-72 ( $M=52.71$ ,  $SD=10.97$ ), and years of education ranged from 9-19 ( $M=13.86$ ,  $SD=2.3$ ). All participants identified themselves as Caucasian. One participant identified as Hispanic/Latino(a), while 55 participants identified as Non-Hispanic/Latino(a).

**Participant Inclusion Criteria.** Participants were required 1) to be 18 years and older and 2) have been diagnosed with manifest Huntington's disease. The HD diagnosis was defined as ever having a rating of a “4” on the Unified Huntington’s Disease Rating Scale (UHDRS) Diagnostic Confidence Interval (“motor abnormalities that are unequivocal signs of HD ( $\geq 99\%$  confidence)”) and either had genetic testing with a positive result for the expanded CAG repeat or a family history of HD with clinical confirmation by a movement disorder specialist. It was also preferred that the participant had an informant who was willing to participate in the study.

**Participant Exclusion Criteria.** Individuals were excluded who 1) had a diagnosis of another neurologic disorder other than HD, 2) were unable to complete questionnaires either due to difficulties with reading the English language or significant impairment that hindered the ability to complete the study protocol (i.e. in the advanced stage of dementia), or 3) were unable to provide informed consent to be part of the study. The Montreal Cognitive Assessment (MoCA) was used to help determine whether or not an individual had the cognitive ability to provide informed consent for the study. Karlawish et al. (2013) reported that a score of 22 on the MoCA provided good sensitivity (94%) in detecting Parkinson’s patients deemed not capable of providing consent (Karlawish et al., 2013). Therefore, individuals with scores  $\geq 22$  were considered capable of providing consent for the study. For those who scored less than 22, the capacity to consent was determined by a health care professional on the study team. These potential participants had to demonstrate that they understood what was explained to them in the consent form by explaining key points of the study related procedures and that they understood the risks and benefits of the study. Additionally, they needed to demonstrate that they understood

that their decision to participate in the study was voluntary and they needed to explain why they would like to participate.

### **Participant Characteristics – Informants**

In the final sample, 55 of the 56 participants identified informants. If more than one caregiver or informant was identified and wanted to participate, the informant who spent the most time with the patient was asked to participate. Forty-one informants completed the study procedures in person and nine completed the procedures through Qualtrics Survey Software, a secure, online survey website. Five identified informants did not complete the survey. In the final sample of 50 informants, there were 24 males (48%) and 26 females (52%), ages ranged from 18-72 ( $M=52.24$ ,  $SD=14.44$ ), and years of education ranged from 10-20 ( $M=14.24$ ,  $SD=2.68$ ). There were no differences in age or education between the patient or informant groups (See Table 1).

One informant identified as African American, one identified as mixed race, and 48 identified as Caucasian. One informant identified as Hispanic/Latino(a), while 49 participants identified as Non-Hispanic/Latino(a). Informants were asked if they themselves were at risk of developing Huntington's disease. When multiple informants were available, informants who had no family history of HD were preferred. Forty-three informants were not at risk because they were unrelated to the patient (i.e. they had no family history of HD). Five informants were at risk, meaning that they have a family history of HD, but were never tested for the gene. One informant was gene-negative, meaning she had a family history of HD but had a negative genetic test result. One informant had presymptomatic HD, meaning the informant tested positive for the HD gene but had not yet developed manifest HD. The informants had the following relationships

to the patients: 27 spouses, 7 children, 6 parents, 3 non-married significant others, 2 siblings, 2 ex-spouses, and 2 nieces, 1 friend. Informants knew the patients for an average of 29 years (SD=14.68; Range: 1 year – 66 years). Informants were also asked to rate how well they knew the information on a Likert scale based on the one used in Hoth et al., 2007 (See Table 2).

**Table 1.** Comparison between patient and informant demographic information.

<b>Demographic:</b>	<b>Patient</b>	<b>Informant</b>	<b>Difference</b>
<b>Age</b>	Mean: 52.71 (10.97)	Mean: 52.24 (14.44)	Not Significant
<b>Education</b>	Mean: 13.86 (2.3)	Mean: 14.24 (2.68)	Not Significant
<b>Gender</b>	20 Male / 36 Female	24 Male / 26 Female	
<b>Ethnicity</b>	1 Hispanic/Latino(a) 55 Non-Hispanic/Latino(a)	1 Hispanic/Latino(a) 49 Non-Hispanic/Latino(a)	
<b>Race</b>	56 Caucasian	1 African American 1 Mixed 48 Caucasian	
<b>HD Categorization</b>	56 Symptomatic HD	43 Not at risk, No family hx 5 At Risk, family hx 1 Tested gene negative 1 Presymptomatic HD, gene +	

**Table 2.** Relationship Quality Based on Informant Report.

<b>Quality of Knowing the Patient</b>	<b>Number (%) of informants providing rating</b>
<b>Very Well</b>	46 (92%)
<b>Pretty Well</b>	3 (6%)
<b>Fairly Well</b>	1 (2%)
<b>Not So Well</b>	0
<b>Hardly At All</b>	0

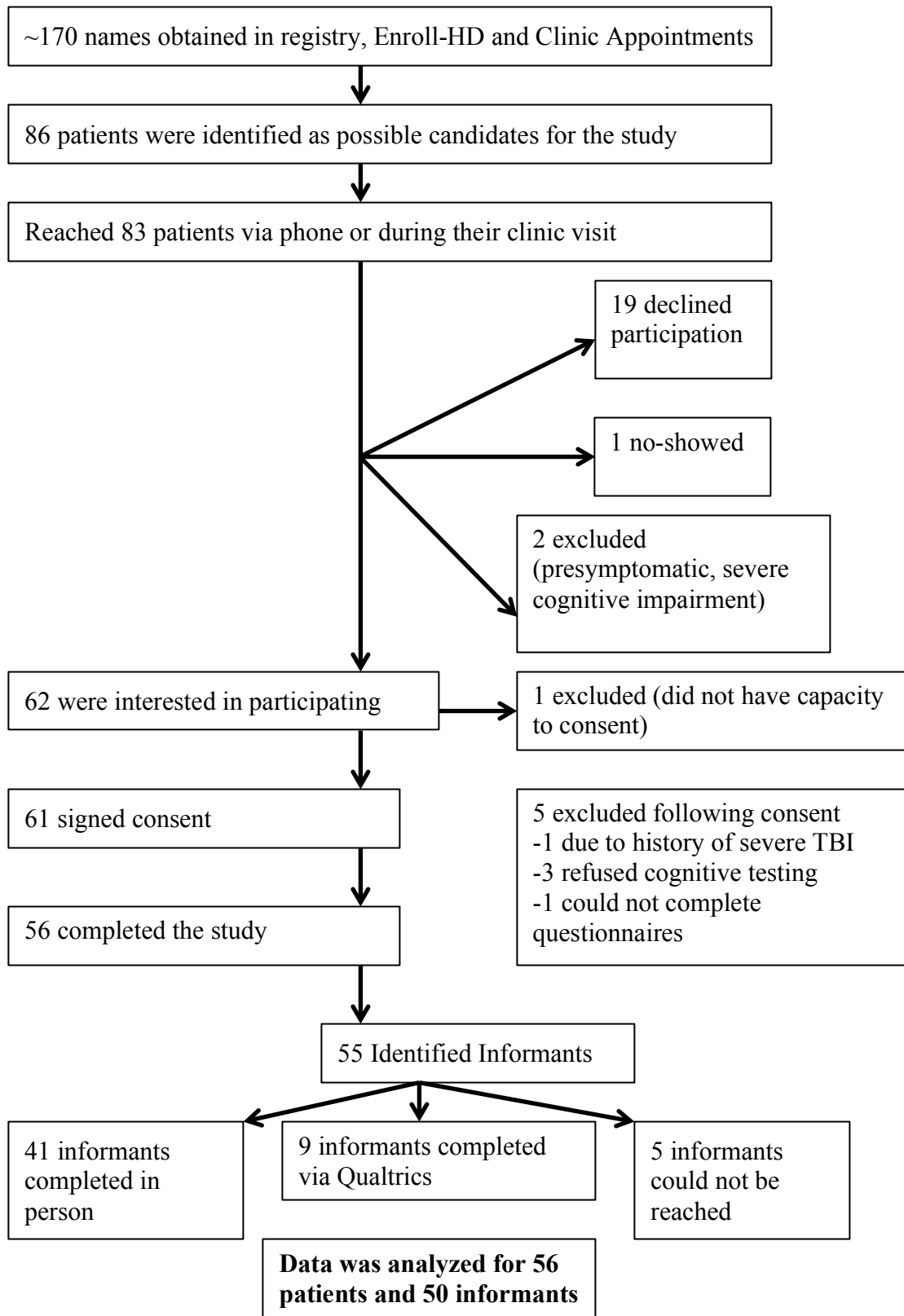
**Informant Inclusion/Exclusion Criteria.** Informants must have 1) been 18 years or older, 2) not have been diagnosed with manifest HD, 3) been capable of providing written, informed consent, 4) must not have been diagnosed with a disorder that is associated with cognitive impairment, 5) had the ability to understand and read English, and 6) if not present at the appointment, must had been able to access questionnaires online and fill out the questionnaires prior to or following the patient’s visit.

### **Participant Recruitment**

HD patients who met the inclusion criteria and also provided consent to be a part of the USF Huntington’s Disease Research Registry (IRB # Pro00010382) or part of the multi-site Enroll-HD study were identified and contacted via phone to gauge interest in participation in the study. Participants were able to complete study procedures before or following their regular clinic visit with their neurologist or before or following another study (i.e. Enroll-HD). (See Figure 4 and Table 3). Patients who were not enrolled in the registry or the Enroll-HD study were approached by their HD neurologist, Juan Sanchez-Ramos, Ph.D., M.D. during their clinic visit. If the patient was willing to hear more about the study, study staff explained the study to them by verbally going through the consent. Staff obtained written consent if the patient and informant were interested in participating. This discussion took place in a private room.

**Table 3.** Patient Recruitment Information for Final Sample.

<b>Recruitment Source</b>	<b>Number of Enrolled Participants Recruited From Source</b>
<b>Enroll – HD Study</b>	37 (66%)
<b>USF HD Research Registry</b>	6 (11%)
<b>Neurology Clinic</b>	13 (23%)



**Figure 4.** Recruitment Flow-Chart.



## Measures

### Self-Report Measures

*The Frontal Systems Behavior Scale; Self and Family Rating Forms (After-Illness Ratings)* were used to assess patient and informants' perception of current frontally mediated behaviors of the patient to assess Metacognitive Knowledge of Apathy and Executive Dysfunction. It is a 46-item questionnaire with subscales that assess Apathy, Disinhibition, and Executive Dysfunction.

Patients and informants rated frontally mediated behaviors on a five-point scale (1=almost never to 5=almost always). T-scores greater than 65 indicate clinical significance. It has been shown to have adequate internal reliability for Total scores (Cronbach's  $\alpha = .88$ ) and Apathy (Cronbach's  $\alpha = .72$ ), Disinhibition (Cronbach's  $\alpha = .75$ ), and Executive dysfunction (Cronbach's  $\alpha = .79$ ) subscales. Adequate internal reliability has also been found for the Family Form Total score (Cronbach's  $\alpha = .92$ ) and Apathy (Cronbach's  $\alpha = .78$ ), Disinhibition (Cronbach's  $\alpha = .80$ ), and Executive dysfunction (Cronbach's  $\alpha = .87$ ) subscales. The FrSBe has been shown to have good convergent validity with the Neuropsychiatric Inventory. Additionally, FrSBe Family Ratings have been used to discriminate between frontally mediated behavioral syndromes in AD and HD (Stout, Ready, Grace, Malloy, & Paulsen, 2003). For the current study, the measure also had adequate internal reliability for patient Total scores (Cronbach's  $\alpha = .919$ ), Apathy (Cronbach's  $\alpha = .816$ ) Disinhibition (Cronbach's  $\alpha = .79$ ), and Executive Dysfunction (Cronbach's  $\alpha = .815$ ). There was adequate consistency for the informant Total scores (Cronbach's  $\alpha = .929$ ), Apathy (Cronbach's  $\alpha = .845$ ), Disinhibition, (Cronbach's  $\alpha = .847$ ), and Executive Dysfunction (Cronbach's  $\alpha = .875$ ).

*Everyday Memory Questionnaire- Revised (Patient and Informant forms)* is a 13-item measure of memory failures in everyday life and was used to measure Metacognitive Knowledge of memory. The 13-item version has two main factors: retrieval and attentional tracking. The measure has been shown to have strong internal reliability (Cronbach's  $\alpha = .89$ ) and good discrimination between clinical and control groups (Royle & Lincoln, 2008). This measure has previously been used to examine awareness of memory functioning in Parkinson's patients (Mack et al., 2013). In this sample, there was adequate internal consistency for both the self-report form (Cronbach's  $\alpha = .939$ ) and the informant-report form (Cronbach's  $\alpha = .934$ ).

*Caregiver Appraisal Scale (Informant Report Only)* is a 28-item questionnaire using a 5-point Likert Scale that assesses four dimensions of caregiving. Adequate reliability has been found for each subscale: caregiving satisfaction (Cronbach's  $\alpha = .87-.77$ ), caregiving mastery (Cronbach's  $\alpha = .73-.52$ ), impact of caregiving (Cronbach's  $\alpha = .78-.77$ ), and subjective caregiving burden (Cronbach's  $\alpha = .91-.89$ ) (Lawton, Moss, Hoffman, & Perkinson, 2000; Struchen, Atchison, Roebuck, Caroselli, & Sander, 2002). Concurrent validity has been demonstrated, as scores on this measure are correlated with other caregiver burden measures. This scale has been used in HD research (Pickett Jr, Altmaier, & Paulsen, 2007). The caregiving burden subscale was used to control for caregiver burden. In this sample, there was adequate internal consistency for the caregiver burden subscale (Cronbach's  $\alpha = .874$ ).

### **Clinician Administered Measures**

*Apathy Evaluation Scale - Clinician Version (AES-C)* is an 18-item clinician administered semi-structured interview of global Apathy. Subscales include cognitive, behavioral, and emotional

Apathy. Internal reliability has been shown to be adequate (Cronbach's  $\alpha = .86-.94$ ). Test-retest reliability varies from  $r = .76$  to  $.94$ . Convergent had been established. The relationship between clinician report and self-report is  $r = .72$ ,  $p < .001$  and clinician and informant report is  $r = .62$ ,  $p < .001$ . The measure has been shown to discriminate from clinician-rated depression,  $r = .39$ ,  $p < .001$  and clinician-rated anxiety,  $r = .35$ ,  $p < .01$  (Marin, Biedrzycki, & Firinciogullari, 1991). This measure was used as a predictor variable of awareness. In this sample, there was adequate internal consistency for the total score (Cronbach's  $\alpha = .905$ ).

### **Huntington's Disease Diagnostic and Neurologic Measures**

*Unified Huntington's Disease Rating Scale – Motor Scale* is a 15-item neurological movement scale administered by a movement disorder specialist with high ratings indicating greater severity of motor symptoms. High internal consistency (Cronbach's  $\alpha = .95$ ) and intercorrelations between domains of the UHDRS have been found. It has also high interrater reliability (intraclass correlation coefficient =  $.94$  for total motor score) (Kremer & Huntington Study Group, 1996). This measure was used to control for disease progression.

*Unified Huntington's Disease Rating Scale – Diagnostic Confidence Interval* is a confidence interval rating given by a trained movement disorder specialist that indicates the level of certainty that the motor abnormalities observed during the motor exam are signs of Huntington's disease. Ratings range from 0-4, with 0 being normal, to 4 (motor abnormalities that are unequivocal signs of HD ( $\geq 99\%$  confidence) (Kremer & Huntington Study Group, 1996). This measure was used to determine eligibility for this study. Only those who ever had a rating of a 4 were eligible to participate in the study.

## **Cognitive Measures**

**Screening Measure.** *Montreal Cognitive Assessment (MoCA)* is a cognitive screening measure that examines different areas of cognitive function (i.e. executive function, language, visuospatial, memory, attention, and orientation) that is used to detect cognitive impairment. The MoCA is scored on a 30-point scale, with a score of 26 or above indicating normal performance. The MoCA will be used to determine global cognitive impairment. Test-retest reliability has been reported to be  $r=.92$  and has adequate internal consistency (Cronbach's  $\alpha =.83$ ). In this sample, internal consistency was adequate (Cronbach's  $\alpha =.768$ ). Convergent validity has been demonstrated with a high correlation ( $r=.87$ ) between the MoCA and the Mini-Mental Status Exam (MMSE), another cognitive screening assessment (Hoops et al., 2009; Lezak et al., 2012; Nazem et al., 2009). It has been suggested that for HD, the MoCA may be a more sensitive screening tool than the MMSE because the MoCA is better suited to capture certain cognitive functions, such as executive functioning (Mickes et al., 2010; Videnovic et al., 2010). This measure was used to describe the severity of cognitive impairment of the sample and was used to determine whether or not an individual had the cognitive ability to provide informed consent for the study.

**Executive Functioning Tasks.** *Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER) - Unstructured Task* is a measure of planning, value-based decision-making, self-regulation, and self-monitoring. This measure was used as a predictor variable (Executive Functioning). The examinee is given three booklets with five pages of simple puzzles that take between 4-60 seconds to complete. Each puzzle is worth a different amount of points. Participants have six minutes to earn as many points as possible.

Puzzles have different cost-benefit ratios. Test-retest reliability has been demonstrated to be  $r=.71$ . It has been shown to be correlated with FrSBe scores ( $r=.29$ ) and separates patients from controls ( $F=11.2$ ,  $p<.005$ ) (NIH EXAMINER Manual). The task performance has been shown to be associated with ventromedial prefrontal cortex damage (Robinson, Calamia, Gläscher, Bruss, & Tranel, 2014). The EXAMINER battery has been validated in several neuropsychiatric populations (Kramer et al., 2014). This battery has shown to be sensitive in HD patients (You et al., 2014).

*Stroop Test (Golden Version, 1976)* is a test of inhibition and was used as a predictor variable (Executive Functioning). Participants are given color words that are printed in different color ink and are required to state the color of the ink in which the word is printed. The test takes advantage of the differences in cognitive processing of words versus color identification, with word reading being considered more of an automatic process. This causes interference when trying to name the color of the ink the word is printed in and the prepotent response of reading needs to be inhibited (Golden & Freshwater, 1978; Lezak et al., 2012). Test-retest reliability has been reported as  $r=.86$  (Word),  $r=.82$  (color), and  $r=+.73$  (Word-Color). The Stroop task has been shown to have convergent validity with tasks of inhibition and processing speed, has been shown to have predictive validity of functional status in a follow-up study of vascular dementia patients (Strauss, Sherman, & Spreen, 2006).

*Trail Making A & B (TMT)* is a task involving scanning and visuomotor tracking, divided attention and cognitive flexibility and will be used as a predictor variable (executive functioning). For Part A, participants draw lines to connect numbered circles in consecutive order as fast as possible. Part B requires participants to connect circles with numbers and letters

by alternating between the two types of sets in consecutive order (Reitan & Wolfson, 1985). Test-retest reliability for part A has been shown to range from  $r = .46-.89$  and  $.44-.87$  for part B. Interrater reliability has been reported to be  $.94$  for part A and  $.90$  for Part B (Fals-Stewart, 1992 {Strauss, 2006 #316}). TMT has demonstrated validity, with significant relationships between it and performance on several other executive function tasks of attention and set-shifting (Strauss et al., 2006). The test has also been shown to be sensitive to individuals with brain damage (Reitan, 1958).

**Memory Task.** *Hopkins Verbal Learning Test – Revised (HVLT-R)* is an auditory verbal learning task where examinees are required to learn a list of items drawn from three semantic categories. This test was used as a memory predictor variable of awareness. The task involves immediate free recall, delayed free recall, and recognition trials. Test-retest reliability has been shown to range from  $r = .74$  for total recall,  $r = .66$  for delayed recall,  $r = .39$  for retention, and  $r = .4$  for recognition discrimination. Convergent Validity studies indicate that total recall has been shown to be correlated with the Wechsler Memory Scale, Logical Memory I ( $r = .75$ ), and delayed recall was associated with Logical memory II ( $r = .77$ ). HVLT-R Retention score was related to Logical Memory Savings score (Logical memory II divided by Logical Memory I) ( $r = .65$ ). The task has also been shown to adequately discriminate between AD and normal geriatric individuals. Total recall in AD patients resulted in 95% sensitivity and 83% specificity. In VaD a linear combination of total recall resulted in 85% correct classification (Brandt & Benedict, 2001).

**Anticipatory and Emergent Awareness Tasks.** *Neuropsychological Assessment Battery (NAB) Daily Living Tests* (Stern & White, 2003) were developed to be highly congruent with analogous real-world behavior and were developed to have stronger ecological validity than

other clinical neuropsychological test measures. The following NAB tasks were used in this study:

- *Driving Scenes Subtest (Attention Module)* is a test where the examinee is shown a series of six driving scenes from behind the steering wheel of a car and needs to indicate which details have changed. The task is associated with visuospatial abilities, working memory, visual scanning, attention to detail, and selective attention. The Driving Scenes test has been shown to be related to an on-road driving test ( $r = .55$ ,  $p < .01$ ) in healthy controls and mild dementia patients, providing some evidence for the ecological validity of the measure (Brown et al., 2005). The Driving Scenes subtest is also related to the WMS-III Digit Span Total ( $r = .32$ ), Letter-Number Sequencing ( $r = .29$ ), Mental Control ( $r = .32$ ), and Working Memory ( $r = .39$ ).
- *Daily Living Memory (Memory Module)* is a task of learning, storage, and free recall of information encountered during everyday functioning. There are two subtasks. The first is the Medication Instructions task, where examinees are presented with instructions for taking medications that they need to remember. The second is the Name, Address, and Phone Number task, where the examinee is to remember these pieces of information. The subtest shows moderate correlations with criterion measures of visual and verbal memory. The retention score is associated with CVLT-II Trials 1-5 total ( $r = .44$ ) and long delay free recall ( $r = .44$ ). The recognition score is associated with CVLT-II Long Delay Recognition ( $r = .39$ ).
- *Judgment (Executive Functioning Module)* is a task that asks examinees questions pertaining to health and safety issues and is associated with problem-solving and knowledge of safety. White and Stern (2003) indicated that judgment is associated with

dorsal-lateral prefrontal cortex and connections to subcortical brain regions. Internal consistency reliability of the measure has been demonstrated (Cronbach's  $\alpha=.83$ ) (MacDougall & Mansbach, 2013). The Judgment subtest is associated with TMT-B score ( $r=.3$ ) and Verbal Fluency ( $r=.46$ ) in a non-impaired sample (Stern & White, 2003).

## **Procedures**

### **Patients Recruited from the Neurology Clinic or HD Research Registry**

Patients who were recruited from the clinic were asked if the data from the Montreal Cognitive Assessment (MoCA) and the Unified Huntington's Disease rating Scale Motor Exam could be used for the study, as these procedures are typically completed during the course of the patients' regular visit. Motor score data were used if the motor exam was completed within one year of the rest of the study procedures, as motor scores have been shown to significantly increase by 6 points after a one year period (Siesling, van Vugt, Zwinderman, Kiebertz, & Roos, 1998). MoCA scores were used if completed within one month of the rest of the study procedures. Nasreddine et al. (2005) have demonstrated high test-retest reliability for the MoCA ( $r=.92$ ,  $p<.001$ ) after one month in healthy controls, mild cognitive impairment and AD patients, with a 0.9 point change in score on average. Additionally, participants were asked for the following demographic information: race, ethnicity, age, gender, highest level of education, age of diagnosis, and onset of motor symptoms and CAG repeat number on the larger allele. Information about current medications that may influence the motor score was obtained (e.g. Xenazine/Tetrabenazine, Risperdal/Risperidone). Patients were asked if their medications have changed if they had completed their clinic visit on a different day than the study procedures. See



Some information was obtained from the patients' medical records if available. Appendix C for detailed demographic information.

### **Participants Who Also Participated in Enroll-HD**

Participants in the Enroll-HD study were asked if the information collected for the Enroll-HD study could be used for this study. This information included demographics, motor exam scores, CAG repeats, medications and cognitive test data (i.e. Trail Making Test). Patients were asked if their medications had changed if they had completed their Enroll-HD visit on a different day. Motor score data was used if the motor exam was completed within one year of the rest of the study procedures. Trail Making Test scores were used if completed within one month of the rest of the study procedures. A study in normal controls indicated no significant change in Trail Making Test scores in a one year period (Basso, Bornstein, & Lang, 1999).

### **Study Procedures for All Participants**

**Patient procedures.** Once enrolled, the participant completed the FrSBe Self-Rating Form (current ratings only) and the Everyday Memory Questionnaire-Revised. Trained study staff administered the AES-C to obtain clinician ratings of Apathy. The trained study staff member also administered the cognitive tests in a counterbalanced order (See Appendix A). The order of whether the participant completed the questionnaires or cognitive tests first was also counterbalanced. Participants used a bell curve from the EXAMINER Battery to examine Anticipatory and Emergent awareness of performance on the NAB tasks. Convergent validity has been demonstrated for bell curve methods in dementia populations; high correlations (above  $r=.8$ ) have been found when comparing verbal prediction ratings and predictions using bell curve

ratings (Williamson et al., 2009). Before and after each NAB task, the participant was asked to evaluate his or her performance by indicating whether he or she was “above average, average, or below average” compared to healthy individuals without Huntington’s disease and who were the same gender, age, and education. The participant then had to indicate where he or she performed on the bell curve. Please refer to Appendix A for the full script that was used.

**Informant procedures.** If the informant was present at the study appointment, the patient and informant were separated to ensure the independence of the report. The study staff reinforced that all data collected was kept confidential. Informants were given a short questionnaire to obtain demographic information (age, education, gender, ethnicity, personal HD status) and about their relation to the patient. These questions are similar to what was used for another study of patient and informant agreement in HD patients (Hoth, 2005; Hoth et al., 2007). See Appendix B for Informant Demographic Questionnaire. The informant completed the following questionnaires: FrSBe-After Illness Ratings (Family Rating Form), Memory Abilities Questionnaire (Informant Rating Form), and the Caregiver Appraisal Form. Informants who completed the online survey signed the consent form electronically. After completion of the study, all participants were debriefed and given the opportunity to ask questions about the study.

**Confidentiality procedures.** Participants were informed that data that was collected was for study purposes and did not have their names or other identifying information associated with it. Only the consent forms contained names. Potential participants were told that their participation in this research was voluntary and the decision to participate would not affect their treatment that they received at the University of South Florida.

## CHAPTER THREE:

### RESULTS

Data were analyzed using IBM SPSS 24.0 for Mac, MPLUS Version 7.2, and SAS 9.4. Please view Appendix D for general data diagnostic information.

#### **Hypothesis One - Metacognitive Knowledge**

*(1) Cognitive Executive Functioning, clinician-rated Apathy, and cognitive Memory will be independently associated with Metacognitive Knowledge of Executive Functioning, Apathy, and Memory as measured by informant and patient discrepancies on self-report measures. (2) Executive Functioning and Memory will be positively associated with Metacognition Knowledge, while Apathy will have a negative association. (3) Apathy and Executive Dysfunction will be more strongly related to Metacognitive Knowledge than Memory.*

#### **Main Proposed Analysis for Hypothesis One**

A multivariate multiple regression approach using a path analysis framework in MPLUS 7.2 was used to determine if cognitive Executive Functioning, Memory performance, and clinician-rated Apathy independently predicted Metacognitive Knowledge of Apathy, Executive Dysfunction, and Memory. The benefit of using this approach was to compare relationships across the individual regression analyses. Multiple imputation was used to maximize the data set

(see Appendix D). Metacognitive Knowledge scores for Apathy and Executive Dysfunction were calculated by subtracting the norm corrected-informant ratings from the norm-corrected patient ratings of the FrSBe Apathy and Executive Dysfunction subscales. Metacognitive Knowledge scores for Memory were calculated by separately adding items from the EMQ-R self and informant reports to create two separate total scores and then subtracting informant scores from patient scores. Five informants had missing items on the EMQ-R and their final scores were prorated. Correlations among predictor and outcome variables were explored. Please view Appendix E for results of correlational analyses.

In the multivariate multiple regression model, the Unstructured Task Standard Score, Stroop Interference score, the HVLTR Recognition Memory raw score, and the AES-C total score were added to the model as the predictors. TMT scores were removed from all analyses to improve power because it was unrelated to any awareness variable in the correlational analyses. The original intended analysis was to complete a principle components analysis of the TMT-B/A Ratio Adjusted score, Stroop Interference Standard Score, and the Unstructured Task Total Points standard score to create a latent executive function variable. This variable was to be used in the multivariate multiple regression analysis for the purpose of improving power. However, the assumptions for PCA or creation of a composite score were not met because the three variables did not have significant relationships with one another.

The following variables were added to control for demographic and disease characteristics: age, education, gender, UHDRS motor score, and Subjective Caregiver Burden subscale score from the Caregiver Appraisal Scale. The outcome variables (Metacognitive Knowledge) were the Apathy (FrSBe), Executive Dysfunction (FrSBe), and Memory (EMQ-R)

discrepancy scores. Scores were converted to z-scores so all variables would be on the same scale.

**Examination of assumptions for regression for Hypothesis One.** Tests of multivariate normality suggested the residuals for the model did not statistically deviate from multivariate normality,  $B_{1p}=0.76$ ,  $X^2(10)=6.81$ ,  $p=0.74$ ,  $B_{2p}=13.64$ ,  $z_{upper}=-1.24$   $z_{lower}=-1.63$ . One data point was identified as a multivariate outlier (Mahalanobis Distance=11.78;  $p<.01$ ). The removal of this data point did not change the results, so it was included in the final analysis. Assumptions were also examined for each OLS regression model. Examination of scatterplots of the standardized residuals, the standardized predicted values, and histogram plots of residuals suggested that the assumptions of random errors, homoscedasticity, and linearity were met. The Watson and Durbin test indicated that residuals were independent (values=2.12, 2.14). Guidelines by Field (2009) were used to examine data points that may be outliers or unduly influential to the model. There were no Cook's d values greater than 1, nor were there any data points with large leverage values. No data points were considered to be casewise outliers ( $\pm 2SD$  from the mean). However, three participants had large Mahalanobis distance values ( $>15$ ). Data analysis was completed with and without these participants to determine if their inclusion in the analysis significantly changed the results. One participant's data changed several predictors from non-significant to significant when the data was included in the model. Therefore, it appears that this one participant seems to be influencing the model's results and was removed from the final analysis. The other two participants' inclusion or exclusion did not change the results, therefore, they were included in the model to maximize the dataset. The results are reported with 48 patient/informant pairs (Table 4).

Examination of VIF and Tolerance values did not reveal serious problems with multicollinearity, however, there were potential issues with multicollinearity for the Unstructured Task total points standard score (VIF=2.6, Tol=.38) and UHDRS Total Motor Score (VIF=3.4, Tol=.297). The Unstructured Task score and UHDRS Motor Score total were highly correlated ( $r=-.689$ ,  $p<.001$ ). One method for handling multicollinearity is to remove one of the variables that are problematic (Field, 2009). Given that the Unstructured Task total points score is one of the main variables of interest, it was not ideal to remove it from the model. A hierarchical regression approach for each outcome variable (Apathy discrepancy, Executive discrepancy, and Memory discrepancy scores) was used to determine if motor scores explained significant additional variance above and beyond the other variables in each of the OLS models as well as to examine if the inclusion or exclusion of motor scores changed the results. Motor scores did not explain additional variance in any of the individual OLS models (See Table 20 in Appendix E). The Unstructured Task is a written task and is likely dependent on motor functioning, which may explain the multicollinearity. Regardless, results presented include motor scores to continue to have a representation of disease progression in the model.  $R^2$  were provided for each individual regression model: Metacognitive Knowledge of Apathy,  $R^2 = .411$ ,  $p<.001$ ; Metacognitive Knowledge of Executive Dysfunction,  $R^2 = .328$ ,  $p<.01$ , and Metacognitive Knowledge of Memory,  $R^2 = .286$ ,  $p<.05$ . See Table 3 and Figure 10 for results. Results of the model without motor scores are provided in Appendix E.

**Hypothesis One: Metacognitive Knowledge regression results.** The Chi-square test of model fit indicated that the saturated model fit significantly better than the model with regression coefficients constrained to 0 for the model with motor scores,  $\chi^2(27)=52.614$ ,  $p<.01$ .

**Table 4.** Metacognitive Analysis with motor scores (48 participants).

	Apathy Awareness			Executive Awareness			Memory Awareness		
	Est.	SE	St. Est	Est.	SE	St. Est	Est.	SE	St. Est.
<i>Uns. Task</i>	<i>0.343</i>	<i>0.227</i>	<i>0.270</i>	<i>0.413+</i>	<i>0.247</i>	<i>0.319+</i>	<i>0.128</i>	<i>0.265</i>	<i>0.1</i>
<i>Stroop Int.</i>	<b><i>0.487*</i></b>	<b><i>0.215</i></b>	<b><i>0.316*</i></b>	<i>0.137</i>	<i>0.234</i>	<i>0.087</i>	<i>0.036</i>	<i>0.251</i>	<i>0.02</i>
<i>AES-C</i>	<b><i>0.260*</i></b>	<b><i>0.131</i></b>	<b><i>0.265*</i></b>	<i>0.226</i>	<i>0.143</i>	<i>0.226</i>	<i>0.103</i>	<i>0.153</i>	<i>0.1</i>
<i>HVLT-R</i>	<i>-0.218</i>	<i>0.137</i>	<i>-0.232</i>	<b><i>-0.347*</i></b>	<b><i>0.149</i></b>	<b><i>-0.362*</i></b>	<b><i>-0.36*</i></b>	<b><i>0.160</i></b>	<b><i>-0.4*</i></b>
Age	-0.002	0.012	-0.020	-0.023+	0.013	-0.266+	-0.03+	0.014	-0.3+
Gender	<b><i>-0.55*</i></b>	<b><i>0.257</i></b>	<b><i>-0.28*</i></b>	0.069	0.280	0.035	0.018	0.300	0.01
Education	0.06	0.055	0.141	0.007	0.060	0.015	0.076	0.065	0.17
CB	-0.24+	0.139	-0.25+	-0.279+	0.151	-0.284+	<b><i>-0.41*</i></b>	<b><i>0.162</i></b>	<b><i>-0.4*</i></b>
UHDRS	-0.07	0.193	-0.08	-0.084	0.210	-0.086	0.02	0.23	0.02

*Main Predictors are italicized; \* p<.05; + p<.1; Uns. Task = Unstructured Task Total Points*

*Standard Score; Stroop Int.=Stroop Interference Scores; HVLT-R=HVLT-R Recognition Scores;*

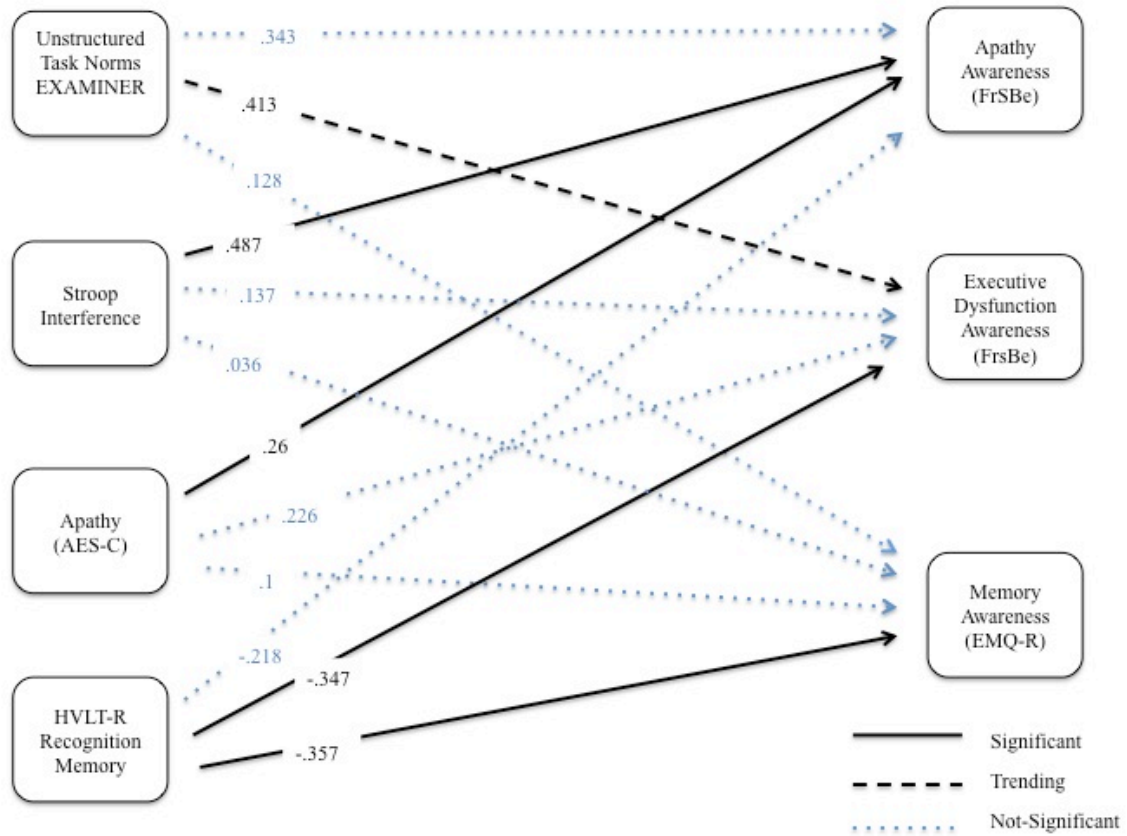
*CB= Caregiver Burden; UHDRS=UHDRS Motor scores*

*Metacognitive Knowledge: Apathy.* There were positive relationships of the Metacognitive Knowledge of Apathy with both the Stroop interference score (positive relationship predicated) and AES-C total score (negative relationship predicted). The Unstructured Task total scores coefficient was no longer significant when motor scores were included in the model. The coefficients for the Stroop and AES-C were not significantly different from each other, Wald Test  $\chi^2 (1)=0.774, p=0.38$ .

*Metacognitive Knowledge: Executive Dysfunction.* The HVLT-R was negatively associated with the discrepancy score for Metacognitive Knowledge of Executive Dysfunction

(positive association predicted). There was a trending, positive relationship between the Metacognitive Knowledge Executive Dysfunction score and the Unstructured Task (positive relationship predicted).

*Metacognitive Knowledge: Memory.* The Metacognitive Knowledge Memory score was only associated with the HVLT-R (negative relationship) recognition predictor variable (positive relationship was predicted).



**Figure 5.** Multivariate Multiple Regression Results.

*Black indicates significant path, Blue indicates non-significant path. Standardized coefficients are reported in the figures.*



## **Exploratory Analyses of Metacognitive Knowledge**

In examining the results of the multivariate multiple regression, it appears that the statistic was underpowered as several variables that were not significant in the simple correlational analyses (See Appendix E) became significant in the regression, indicating possible suppressor effects. Another difficulty is in the interpretation of difference scores in the regression analysis. When examining individuals' difference scores, negative scores indicate that the informant rated the symptom more severely than the patient. Positive difference scores indicate that the patient rated the symptom more severely than the informant. Because of this, a positive relationship between the discrepancy scores and cognition does not necessarily indicate better cognition with better awareness, nor does a negative relationship indicate worse awareness with worse cognition (or the opposite with Apathy). For example, a positive relationship between the Stroop and Awareness of Apathy does not necessarily indicate that better awareness is associated with Stroop performance. It could alternatively indicate that for those with high informant ratings (negative difference scores), better Stroop scores could indicate better awareness. However, those with high patient ratings, the patients with the best Stroop performance are actually overestimating their symptom severity relative to the informant. There may also be a relationship only when informants are rating the patient more severely, but not when the patients are providing more severe ratings. While the correlational analyses can be further examined via scatter plot to determine the nature of these relationships, significant regression coefficients indicate that there is some kind of relationship between the variables, but the nature of the relationship is difficult to determine.

Given the null correlational results and use of difference scores, the regression is difficult to interpret. Additional analyses were conducted to explore Metacognitive Knowledge in

Huntington's disease to circumvent this issue with difference scores. These analyses provided interesting results that align with the expected hypotheses and past work in this area.

**Exploratory analysis: Comparing patient and informant ratings (49 participants).**

Mean Apathy outcome (Patient:  $M=71.67$ ,  $SD=19.15$ ; Informant:  $M=87.96$ ,  $SD=19.36$ ) and Executive Dysfunction outcome (Patient:  $M=73.8$ ,  $SD=17.35$ ; Informant:  $M=75.67$ ,  $SD=15.99$ ) group scores based on FrSBe subscales were above clinical cut-offs ( $T=65$ ) for both patient and informant ratings. The mean patient EMQ-R score was 24.16 (16.23), while the mean informant EMQ-R score was 20.7 (13.96). Paired t-tests were used to examine if there were mean differences in ratings of Apathy, Executive Dysfunction, and Memory between patient and informant groups. The mean Apathy informant rating was significantly higher than the mean patient Apathy rating,  $t(48)=5.35$ ,  $p<.001$ . There were no significant mean differences between patient and informant ratings of Executive Dysfunction or Memory.

Further analysis was completed to determine if the differences between patient and informant report varied as a function of symptom severity. Splitting the sample based on motor score severity was initially considered given motor scores could represent disease severity. However, 48% of the patients were on medication to control movements, which could impact their motor scores. Therefore, one set of analyses was conducted using informant ratings to split the sample and a second set of analyses was conducted using the MoCA scores to split the sample based on overall cognitive functioning.

Informant ratings for Apathy, Executive Dysfunction and Memory were divided into tertiles. The bottom tertile represented lower informant rated symptom severity while the top represented the highest informant rated symptom severity. Differences between patient and

informant ratings were analyzed across these tertiles using a 2 (patient/informant report) X 3 (tertiles 1 through 3) mixed model analysis of variance.

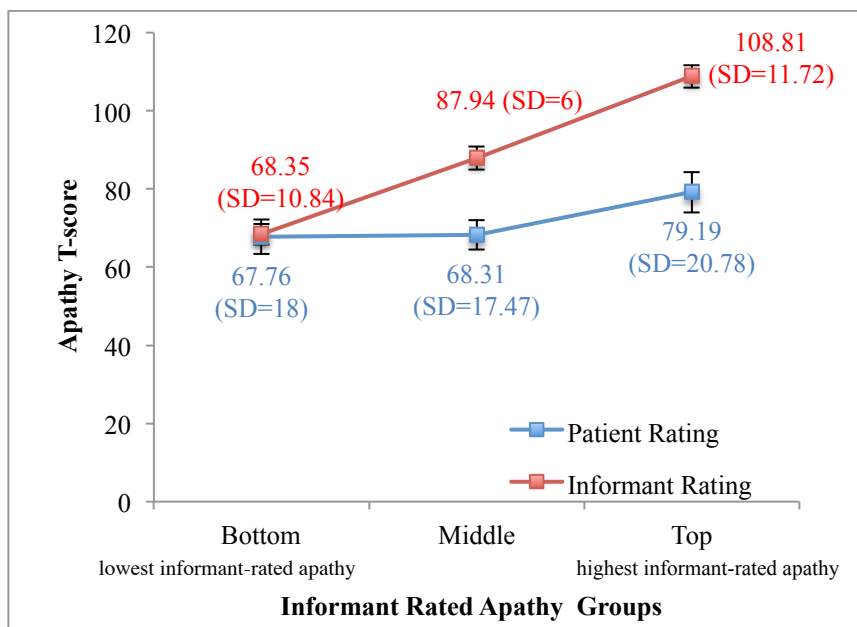
*Apathy.* The results revealed a two-way interaction between type of report and group,  $F(2, 46) = 11.36, p < .001$ , with main effects for tertile group,  $F(2, 46) = 19.2, p < .001$  and report type  $F(1, 46) = 42.53, p < .001$ . In post-hoc analysis, there was no significant difference between the patient and informants for the lowest Apathy group, however, informants rated Apathy significantly higher than the patients for the middle  $t(15) = 4.786, p < .001$  and most severe groups  $t(15) = 6.192, p < .001$  (See Figure 6). Differences in predictor variable values were examined between top and bottom groups using independent samples t-tests. There was a significant difference between total AES-C scores  $t(21) = 2.18, p < .05$  with the bottom group (lowest Apathy) ( $M = 42.24, SD = 12.89$ ) having lower clinician rated Apathy than the top group (highest Apathy) ( $M = 50.88, SD = 9.51$ ). There was also a significant difference in Stroop performance  $t(31) = 2.3, p < .05$ , with the top group (highest Apathy) ( $M = 46.31, SD = 3.07$ ) performing worse than the bottom group (lowest Apathy) ( $M = 50.29, SD = 6.22$ ).

*Executive Dysfunction.* The results revealed a two-way interaction between type of report and tertile group,  $F(2, 46) = 9.06, p < .001$ , with a main effect for tertile group,  $F(2, 46) = 16.28, p < .001$ . Post-hoc analysis revealed that for the lowest informant-rated symptom group – patients rated their Executive Dysfunction more severely than the informants  $t(15) = 2.522, p < .05$ . The middle tertile group was in agreement. For the top group (highest Executive Dysfunction), informants provided more severe ratings compared to the patients  $t(18) = 3.08, p < .01$  (See Figure 7). When examining differences in predictor variables between the top and bottom groups, the top group (most informant-rated Executive Dysfunction) performed significantly worse on TMT-B,  $t(33) = 2.3, p < .05$  (T-scores Top  $M = 19.86, SD = 9.31$ ; Bottom  $M = 35.68, SD = 17$ ) and the

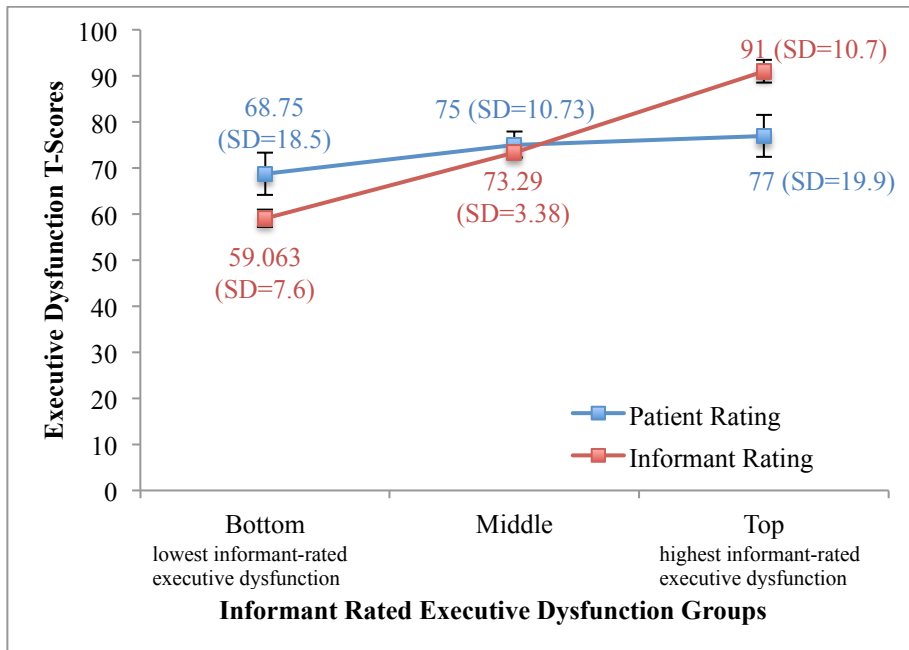
Unstructured Task  $t(33)=2.1$ ,  $p<.05$  (z-scores Top  $M=-1.71$ ,  $SD=.57$ ; Bottom  $M=-1.25$ ,  $SD=.75$ ).

There was significantly lower Apathy for the bottom group  $t(33)=2.73$ ,  $p<.01$  (top:  $M=48.21$ ,  $SD=7.97$ ; bottom:  $M=39.31$ ,  $SD=11.29$ ).

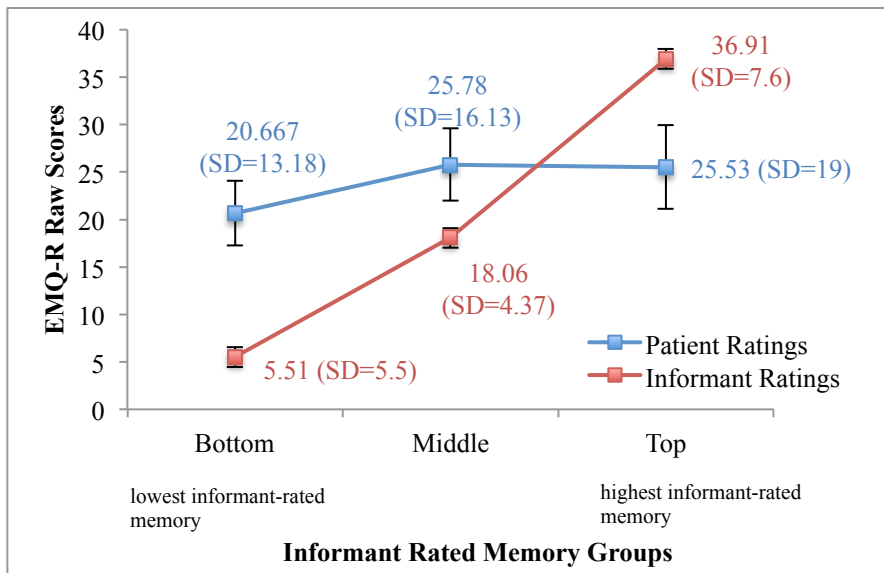
*Memory.* The results revealed a significant two-way interaction between report type and tertile group,  $F(2, 47)= 11.82$ ,  $p<.001$  with a significant main effects for tertile group,  $F(2, 47)=15.17$ ,  $p<.001$ . Patient ratings were significantly higher than informant ratings for the bottom group (lowest informant-rated memory issues),  $t(14)=4.96$ ,  $p<.001$  and middle groups,  $t(17)=2.03$ ,  $p<.05$ , while informant ratings were higher than the patients' in the top group (highest informant-rated memory issues),  $t(16)=2.317$ ,  $p<.05$  (See Figure 8). When comparing predictor variables between top and bottom groups, the top group demonstrated poorer performance on the Stroop,  $t(30)=3.3$ ,  $p<.01$  (top -  $M=44.94$ ,  $SD=4.99$ ; bottom -  $M=51.72$ ,  $SD=6.54$ ) and had significantly worse clinician rated Apathy (AES-C),  $t(30)=2.86$ ,  $p<.01$  (top -  $M=48.47$ ,  $SD=11.46$ ; bottom -  $M=37.73$ ,  $SD=9.56$ ).



**Figure 6.** Mean informant and patient ratings of Apathy based on informant rating tertiles.



**Figure 7.** Mean informant and patient ratings of Executive Dysfunction based on informant rating tertiles.



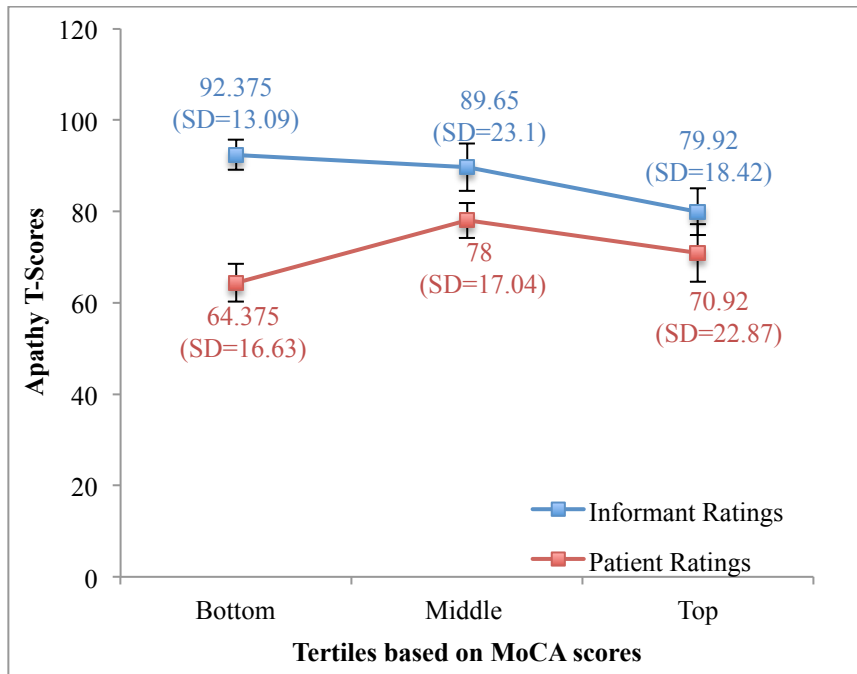
**Figure 8.** Mean informant and patient ratings of Memory based on informant rating tertiles.

**Exploratory analysis: Examining patient and informant agreement based on overall cognitive impairment using the MoCA.** The sample was split into thirds based on MoCA Standard Scores. The Top group had the highest (best) MoCA standard scores (N=16; Mean: .5887, SD=.42), while the bottom group had the lowest (worst) scores (N=13; Mean=-2.36, SD=.8).

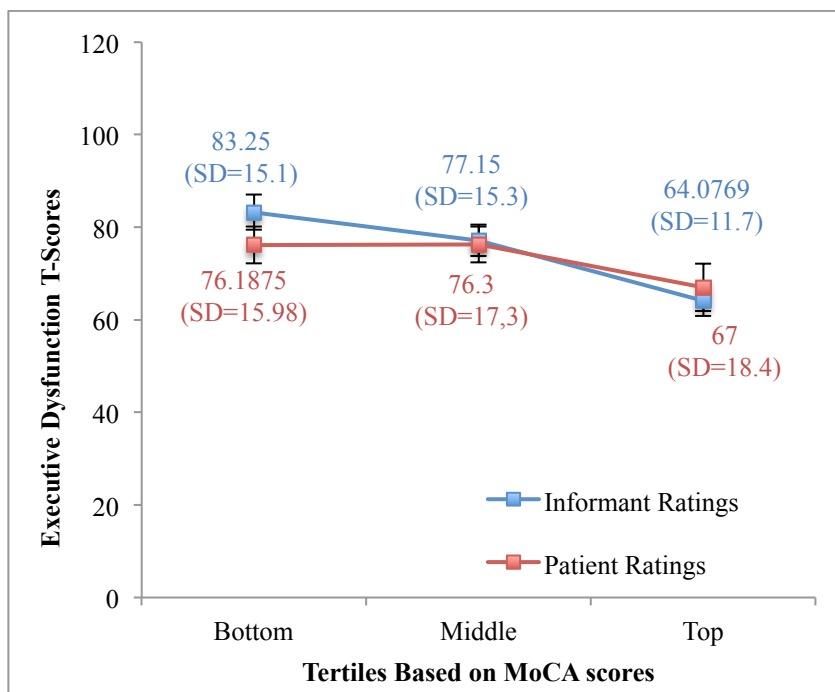
For Apathy ratings, there were significant differences in informant and patient ratings for the bottom two thirds of the sample (bottom,  $t(15)=7.533$ ,  $p<.001$ , middle,  $t(19)=2.369$ ,  $p<.05$ ). There was no difference between patient and informant ratings of Apathy for the best MoCA performers (See Table 5 and Figure 9). There were no significant differences for any of the tertile groups between patient and informant report for Executive Dysfunction (See Figure 10). There were no significant differences for any of the tertile groups between patient and informant report for memory (See Figure 11).

**Table 5.** Apathy ratings for groups based on MoCA scores.

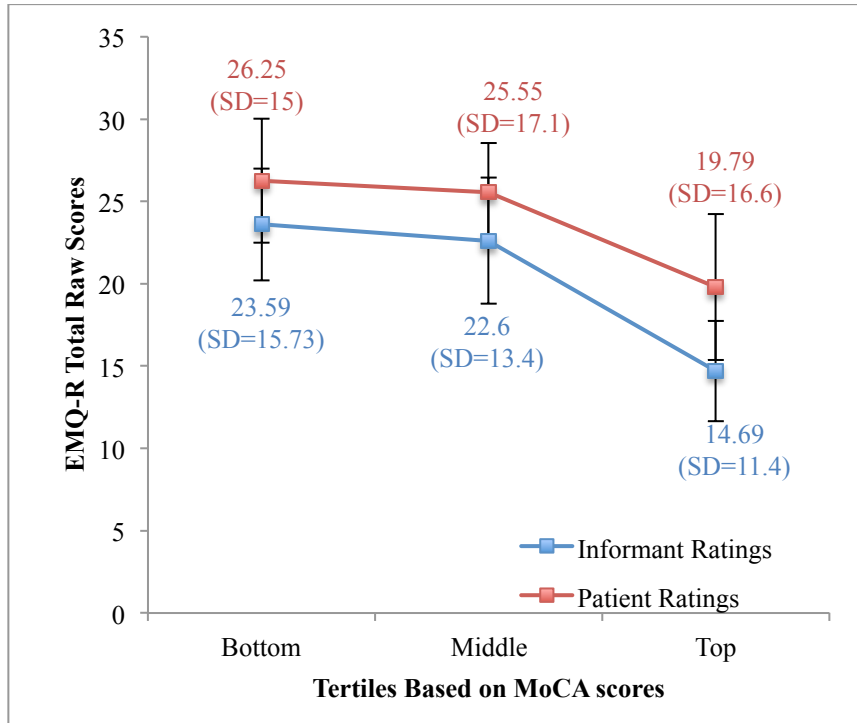
	<b>Bottom</b> <b><math>t(15)=7.533</math>, <math>p&lt;.001</math></b>	<b>Middle</b> <b><math>t(19)=2.369</math>, <math>p&lt;.05</math></b>	<b>Top</b> <b>ns</b>
<b>Patient Mean</b>	64.38 (SD=16.63)	78 (SD=17.04)	70.92 (SD=22.87)
<b>Informant Mean</b>	92.38 (SD=13.09)	89.65 (SD=23.1)	79.92 (SD=18.42)



**Figure 9.** Informant and patient ratings of Apathy based on patient performance on the MoCA.



**Figure 10.** Informant and patient ratings of Executive Dysfunction based on patient performance on the MoCA.



**Figure 11.** Informant and patient ratings of Memory based on patient performance on the MoCA.

**Exploratory analysis of Metacognitive Knowledge: Associations between cognitive performance and self-report ratings (49 participants).** Patient self-reported memory was negatively associated with delayed memory performance, recognition memory, and percent retention, therefore worse self-reported memory was associated with lower actual memory performance on cognitive testing. Informant report of the patients' Memory was only negatively associated with delayed memory. Informant report of the patients' Executive Dysfunction was negatively associated with performance on executive function tasks (i.e., Unstructured Task, Trail Making Test, and Stroop Test) while there was no association between patient ratings of Executive Dysfunction and executive function performance (See Table 6).



Additionally, when examining patient and informant report of Apathy, only informant report was related to cognitive performance on executive functioning tasks (TMT-B standard score ( $r=-.322$ ,  $p<.05$ ); Stroop CW Standard ( $r=-.351$ ,  $p<.05$ )).

**Table 6.** The Relationship Between Patient and Informant Reports and Neuropsychological Test Results.

<b>Memory – Everyday Memory Questionnaire</b>		
<b>Neuropsych Task</b>	<b>Patient Report</b>	<b>Informant Report</b>
HVLT-R Immediate Trials	ns	ns
HVLT-R Delay	$r=-.292$ , $p<.05$ (Raw) $r=-.311$ , $p<.05$ (T Score)	$r=-.26$ , $p=.066$ (Raw) $r=-.29$ , $p<.05$ (T Score)
HVLT-R Recognition	$r=-.459$ , $p<.001$ (Raw) $r=-.408$ , $p<.01$ (T Score)	ns
Percent Retention	$r=-.289$ , $p<.05$ (Raw) $r=-.398$ , $p<.01$ (T Score)	ns (Raw) $r=-.27$ , $p=.06$ (T Score)
<b>Executive Function- FrSBe Executive Dysfunction Subscale</b>		
<b>Neuropsych Task</b>	<b>Patient Report</b>	<b>Informant Report</b>
Unstructured Task Points (z)	ns	$r=-.328$ , $p=.05$
Stroop Color-Word	ns	$r=-.475$ , $p<.001$
Stroop Interference	ns	$r=-.346$ , $p=.05$
TMT B Time	ns	$r=-.361$ , $p<.05$
TMT B Standard Score	$r=-.321$ , $p<.05$	$r=-.426$ , $p<.01$
TMT B-A (z)	ns	$r=-.26$ , $p=.071$
TMT B/A Ratio (z)	ns	ns
<b>Apathy – FrSBe Apathy Subscale</b>		
<b>Neuropsych Task</b>	<b>Patient Report</b>	<b>Informant Report</b>
Stroop Color-Word	ns	$r=-.351$ , $p<.05$
TMT B Standard Score	ns	$r=-.322$ , $p<.05$

*ns=not significant; standard scores reported except where indicated; z=z-score.*

## **Hypothesis Two - Anticipatory Awareness**

*(1) Cognitive Executive Functioning, clinician-rated Apathy, and cognitive Memory will be independently associated with Anticipatory Awareness of Executive Functioning and Memory as measured by performance prediction on tasks of everyday functioning. (2) Executive*

*Functioning and Memory will be positively associated with Anticipatory Awareness while Apathy will be negatively associated. (3) Apathy and Executive Dysfunction will have stronger relationships with Anticipatory Awareness than Memory.*

**Validity Check for Performance Prediction (Anticipatory Awareness) and Evaluation (Emergent Awareness) Rating Method**

To demonstrate that patients’ ratings on the bell curve were consistent with their beliefs (i.e Anticipatory and Emergent Awareness), patients were asked to provide a verbal indicator of their performance (i.e. average, above average, or below average) in addition to a percentile rating.

**Table 7.** Kendall’s Tau Correlations: Verbal statement of ratings and percentile ratings using the bell curve method.

NAB Task	Performance Prediction Rating /Anticipatory Awareness	Performance Evaluation Rating/ Emergent Awareness
<i>Driving</i>	.847**	.743**
<i>Judgment</i>	.765**	.793**
<b>Medication</b>		
<i>Immediate Memory</i>	.756**	.660**
<i>Delay Memory</i>	.731**	.704**
<i>Recognition Memory</i>	.773**	.802**
<b>Address</b>		
<i>Immediate Memory</i>	.799**	.679**
<i>Delay Memory</i>	.717**	.687**
<i>Recognition Memory</i>	.797**	.834**

\*\* indicates  $p < .0001$

Patients' verbal ratings of their performance were strongly correlated with their percentile ratings for all NAB tasks, suggesting that patient's ratings were consistent with their beliefs of performance (see Table 7).

### **Main Proposed Analysis for Hypothesis Two**

A multivariate multiple regression approach using a path analysis framework was used to explore the hypothesis. The outcome variables were the memory and executive function Anticipatory Awareness factor scores which were calculated by subtracting the patient ratings from the actual performance percentile for each NAB task and/or subtask (See Appendix F for information on the creation of factor scores). The Unstructured Task total points, Stroop Interference score, HVLT-R Recognition Score and AES-C score were the predictor variables. The regression analysis controlled for age, education, gender, and UHDRS motor score. Correlations between predictor and outcome variables were analyzed (See Appendix F for a full report of correlational analyses).

**Regression assumptions and diagnostics.** Tests of multivariate normality suggested that the residuals for the model did not statistically deviate from multivariate normality,  $B_{1p}=1.87$ ,  $X^2(20)=18.18$ ,  $p=0.58$ ,  $B_{2p}=24.81$ ,  $Z_{upper}=.43$ ,  $Z_{lower}=-0.74$ . One multivariate outlier was identified. Regression assumptions were also examined for each OLS regression model. Examination of scatterplots of the standardized residuals and the standardized predicted values suggested that the assumptions of random errors and linearity were met. The Watson and Durbin test indicated that residuals were independent (values=2.12, 2.14). Examination of a histogram of the residuals indicated that the residuals were normally distributed, however, an issue related to homoscedasticity was noted for a few data points. Examination of influential data points revealed

large Mahalanobis distance values (>15) for three cases across all 4 OLS regressions. Upon removal of these cases, scatterplots of the standardized residuals appeared to be a random pattern of points, suggesting the data met the homogeneity of variance assumption for each separate OLS model. Additionally, three casewise outliers were identified. Data changed significantly upon removal of 4 out of the 6 participants that were identified to be casewise outliers or had large Mahalanobis distance values, suggesting they potentially influenced results. Results were therefore examined with 51 out of the 55 participants who had data. Similar to the Metacognitive Knowledge analyses, a potential issue with multicollinearity between the Unstructured Task total points and UHDRS Motor score was identified (Unstructured Task: Tolerance=.4, VIF=2.49; Motor Scores: Tolerance =.36, VIF=2.77). Because inclusion or exclusion of UHDRS motor scores did not change the results of the regression analysis, results with the inclusion of the UHDRS motor scores are reported.

**Anticipatory Awareness: Regression results (51 participants).** The Chi-square test of model fit indicated that the saturated model fit significantly better than the model with regression coefficients constrained to 0,  $\chi^2(32)=56.599$ ,  $p<.01$ .  $R^2$  were provided for each individual regression model for each outcome variable (the Anticipatory Awareness Factor Scores): Executive Prediction  $R^2=.183$   $p=.065$ ; Immediate memory prediction  $R^2=.195$ ,  $p=.052$ , Delay Memory Prediction  $R^2=.327$ ,  $p<.01$ ; Recognition Memory  $R^2=.257$ ,  $p<.05$ . There was a trending, positive relationship with the Executive Anticipatory Awareness Factor Score and the AES-C, and a significant, positive relationship with the HVLT-R recognition score. The Immediate Memory Prediction score had a positive relationship with the AES-C and a negative relationship with the Unstructured Task score.

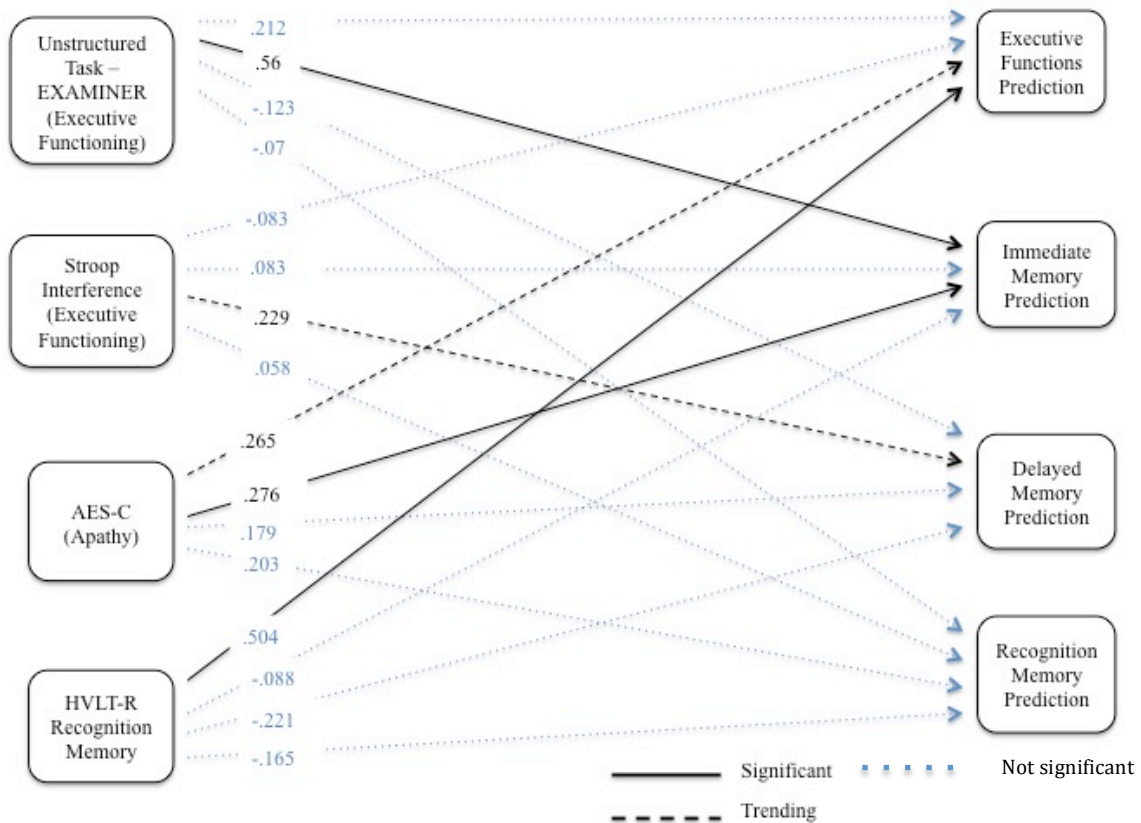
There was a trending relationship with the Delay Memory Prediction score and the Stroop Interference score. See Table 8 and Figure 12 for the complete results.

**Table 8.** Multivariate Multiple Regression for Memory and Executive Anticipatory Awareness (Performance Predictions).

	Executive Prediction			Immediate Memory Prediction			Delay Memory Prediction			Recognition Memory Prediction		
	Est	SE	St.	Est	SE	St.	Est	SE	St	Est.	SE	St.
<i>Uns</i>	<i>0.3</i>	<i>0.3</i>	<i>0.21</i>	<b><i>-0.7</i></b>	<b><i>0.28</i></b>	<b><i>-0.56</i></b>	<i>-0.2</i>	<i>0.271</i>	<i>-0.12</i>	<i>-0.09</i>	<i>0.281</i>	<i>-0.07</i>
<i>Stroop</i>	<i>-0.1</i>	<i>0.2</i>	<i>-0.1</i>	<i>0.13</i>	<i>0.24</i>	<i>0.083</i>	<i>0.4+</i>	<i>0.232</i>	<i>0.2+</i>	<i>0.096</i>	<i>0.242</i>	<i>0.06</i>
<i>AES</i>	<i>0.3+</i>	<i>0.1</i>	<i>0.3+</i>	<b><i>0.28</i></b>	<b><i>0.14</i></b>	<b><i>0.276</i></b>	<i>0.19</i>	<i>0.135</i>	<i>0.18</i>	<i>0.214</i>	<i>0.140</i>	<i>0.2</i>
<i>HVLT</i>	<b><i>0.5</i></b>	<b><i>0.2</i></b>	<b><i>0.5</i></b>	<i>-0.1</i>	<i>0.23</i>	<i>-0.088</i>	<i>-0.2</i>	<i>0.222</i>	<i>-0.22</i>	<i>-0.17</i>	<i>0.224</i>	<i>-0.17</i>
Gender	0.2	0.2	0.16	-0.2	0.33	-0.112	-0.2	0.316	-0.07	-0.21	0.326	-0.10
Motor	0.5+	0.3	0.5+	-0.5+	0.29	-0.51+	<b><i>-0.7</i></b>	<b><i>0.277</i></b>	<b><i>-0.64</i></b>	-0.43	0.289	-0.42
Edu.	0.3+	0.2	0.26	<b>0.14</b>	<b>0.06</b>	<b>0.333</b>	-0.1	0.061	-0.21	0.008	0.063	0.02
Age	-0.3	0.2	-0.2	0.03+	0.02	0.303+	<b>0.05</b>	<b>0.014</b>	<b>0.57</b>	<b>0.05</b>	<b>0.015</b>	<b>0.53</b>

*Italicized are main DVs, Bolded indicates significance p>05, + indicates trending, Uns=*

*Unstructured Task total points, Edu=Education*



**Figure 12.** Model for Multivariate Multiple Regression Analysis: Anticipatory Awareness/Performance Prediction.

*Black indicates significant path, Blue indicates non-significant path. Standardized coefficients are reported in the figures.*

**Hypothesis Three - Emergent Awareness**

*(1) Cognitive Executive functioning, clinician-rated Apathy, and cognitive Memory will be independently associated with Emergent Awareness of Executive Functioning and Memory as*

*measured by performance evaluation on tasks of everyday functioning. (2) Executive functioning and Memory will be positively associated with awareness while Apathy will be negatively associated. (3) Apathy and Executive Dysfunction will be greater contributing factors to Emergent Awareness in HD than Memory.*

### **Main Proposed Analyses of Hypothesis Three**

A multivariate multiple regression approach using a path analysis framework was used to explore the hypothesis. The outcome variables were the immediate, delay, and recognition memory and executive function evaluation factor scores which were calculated by subtracting the patient ratings from the actual performance percentile for each NAB task and/or subtask. The Unstructured Task total points, Stroop interference score, HVLT-R Recognition Score and AES-C score were the predictor variables. The regression model controlled for age, education, gender, and UHDRS motor score.

**Regression assumptions and diagnostics.** Tests of multivariate normality suggests the residuals for the model do statistically deviate from multivariate normality  $B_{1p}=2.14$ ,  $X^2(20)=20.74$ ,  $p=0.43$ ,  $B_{2p}=23.23$ ,  $z_{upper}=-.41$ ,  $z_{lower}=-1.57$ . One multivariate outlier was identified. Examination of a histogram of the residuals indicated that the residuals are normally distributed. Examination of scatter plots of residuals indicated that the assumption of homoscedasticity has been met. Examination of influential data points revealed large Mahalanobis distance values for three cases across all 4 OLS regressions. One of these data points was the same point identified as a multivariate outlier. Additionally, seven casewise outliers were identified across the OLS regressions. The results did not change with the removal of these individuals from the data set. Data is reported with all data points included. Similar to

the previous analyses, a potential issue with multicollinearity between the Unstructured Task total points and UHDRS Motor score was identified (Unstructured Task: Tolerance=.4, VIF=2.49; Motor scores Tolerance =.36, VIF=2.77). Because the inclusion or exclusion of UHDRS Motor scores did not change the results of the regression analysis, results with the inclusion of the UHDRS Motor scores are reported, especially since UHDRS Motor scores were a significant predictor for some of the outcome variables. The Durbin-Watson statistic (values range from 2.09-2.28), which tests the independence of errors assumption, was in the acceptable range.

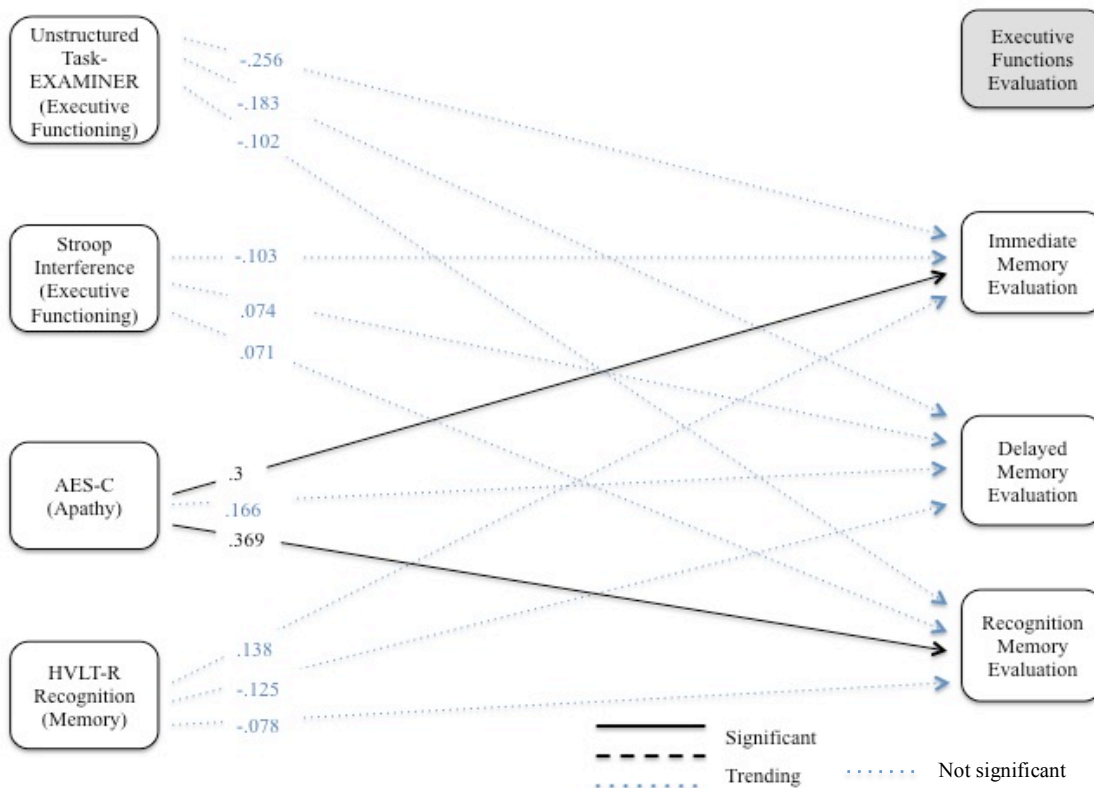
**Table 9.** Multivariate Multiple Regression Analysis: Emergent Awareness (45 Participants).

	Executive Evaluation	Immediate Memory Evaluation			Delay Memory Evaluation			Recognition Memory Evaluation		
		Est	SE	St.	Est	SE	St	Est.	SE	St.
Uns.		-0.341	0.257	-0.256	-0.242	0.236	-0.183	-0.136	0.239	-0.1
Stroop		-0.169	0.239	-0.103	0.120	0.219	0.074	0.117	0.223	0.07
AES-C		<i>0.311*</i>	<i>0.134</i>	<i>0.30*</i>	0.172	0.123	0.166	<i>0.382*</i>	<i>0.125</i>	<i>0.4*</i>
HVLTR		0.147	0.168	0.138	-0.132	0.156	-0.125	-0.083	0.156	-0.1
Gender		-0.042	0.062	0.084	-0.261	0.261	-0.128	0.318	0.266	0.15
Total Motor		-0.279	0.196	-0.279	<b>-0.48*</b>	<b>0.183</b>	<b>-0.48*</b>	-0.319	0.183	-0.3
Education		0.173	0.285	-0.098	-0.10+	0.057	-0.2+	0.059	1.025	0.13
Age		0.015	0.013	0.168	<b>0.043*</b>	<b>0.012</b>	<b>0.48*</b>	<b>0.043*</b>	<b>0.012</b>	<b>0.5*</b>

*Italicized are main DVs, Bolded indicates significance  $p > 0.05$ , + indicates trending*



**Emergent Awareness/Performance Evaluation: Regression results.** The Chi-square test of model fit indicated that the saturated model did significantly fit better than the model with regression coefficients constrained to 0,  $\chi^2(32)=49.278, p<.05$ .  $R^2$  were provided for each individual regression model: Executive Evaluation,  $R^2=$  not significant. Immediate Memory  $R^2=.178, p=.057$ ; Delay Memory  $R^2=.309, p<.01$ ; Recognition Memory  $R^2=.287, p<.01$ . Regarding the primary predictors, only the AES-C had positive relationships with the Immediate and Recognition Memory Evaluation discrepancy scores. When regression was attempted with Driving or Judgment Emergent Awareness score alone rather than combined into a factor score, neither of those regressions were significant. See Table 9 and Figure 13 for complete results.



**Figure 13.** Model for Multivariate Multiple Regression Analysis: Emergent Awareness/Performance Evaluation.

### **Exploratory Analyses for Online Awareness**

Similar to Hypothesis 1, the proposed analyses to test the Online Awareness Hypotheses (Hypotheses 2 and 3) was to use a multivariate multiple regression approach. Initial correlational analyses, however, did not reveal any convincing relationships among the predictor and outcome variables. The multivariate multiple regression was underpowered and suppression effects also arose, making the regression analysis difficult to interpret. Furthermore, difference scores make it difficult to interpret the nature of the relationships observed. Additional analyses were conducted to further explore Online Awareness in HD.

**Exploratory analysis: Relationships between patient ratings and actual performance.** Patients' predictions of executive performance (i.e. Judgment and Driving tasks) were unrelated to actual performance, while memory predictions (i.e. Medication and Address Memory) were related to performance (Anticipatory Awareness). Memory evaluation was more strongly associated with performance than executive function evaluation (Emergent Awareness) (see Table 10).

**Exploratory analysis: Differences between Prediction ratings (Anticipatory Awareness), Evaluation ratings (Emergent Awareness) and actual performance.** Paired-samples t-tests were used to examine if there were mean differences in performance on the NAB memory and executive function tasks and the patients' performance prediction ratings for the tasks. For all NAB tasks, mean predictions were significantly higher than actual performance (all differences  $p < .001$ ).

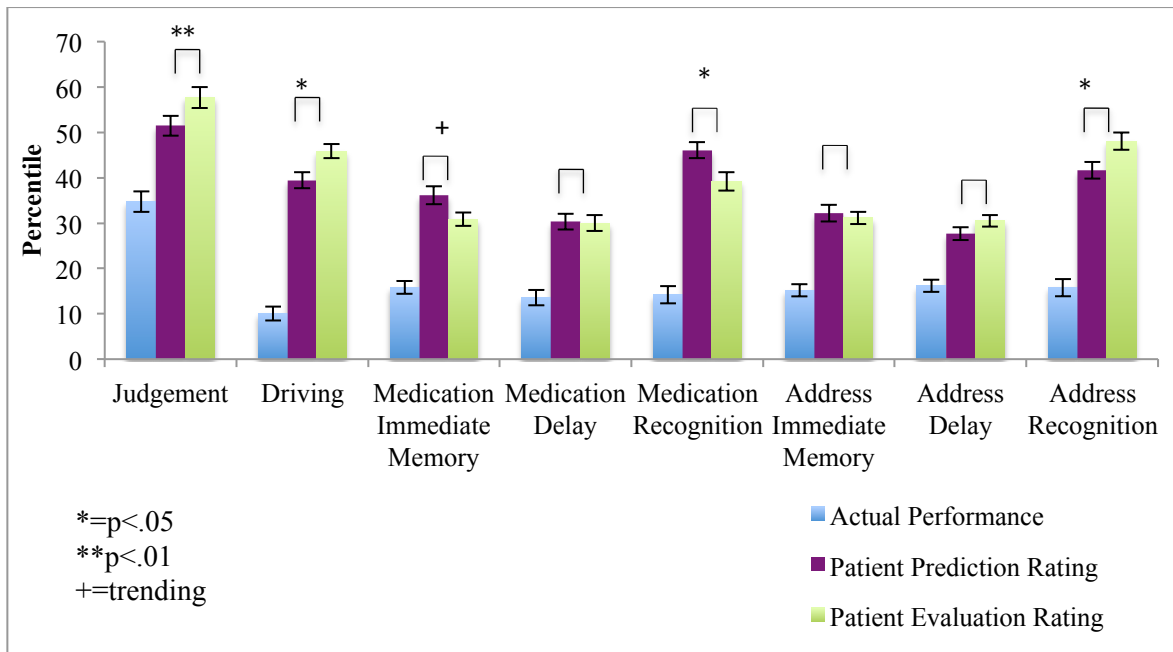
**Table 10.** Relationship between performance prediction (Anticipatory Awareness) and evaluation (Emergent Awareness) percentile ratings and actual performance.

NAB Task:	Performance Prediction	Performance Evaluation
Judgment	ns	ns
Driving	ns	ns
Medication Memory Immediate	ns	$r=.415, p<.01$
Medication Memory Delay	$r=.274, p<.05$	$r=.337, p<.05$
Medication Memory Recognition	$r=.257, p=.058$	$r=.288, p<.05$
Address Memory Immediate	ns	$r=.552, p<.001$
Address Memory Delayed	$r=.512, p<.001$	$r=.594, p<.001$
Address Memory Recognition	$r=.338, p<.05$	$r=.452, p<.001$

When examining differences between performance prediction and evaluation ratings, on average, participants' evaluations of performance were higher than their predictions for the Judgment, Driving and Address Memory Recognition tasks. Their evaluations were lower for the Medication Immediate Memory and Medication Memory Recognition Tasks (See Figure 14).

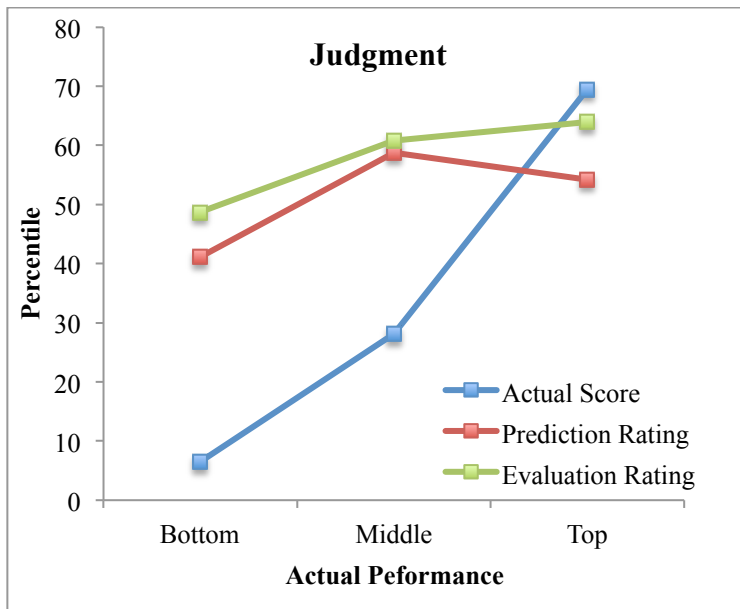
Exploratory analyses were conducted to examine differences among actual performance and predictions and evaluations. Participants were separated into tertile groups based on actual performance. The Bottom group represented the worst performers, while the Top group represented the best performers. Differences were analyzed across these tertiles using a 3 (Score: actual performance, prediction rating, and evaluation rating) X 3 (Tertiles: 1 through 3) mixed

model analysis of variance with special attention to interaction effects to determine if differences in discrepancies between performance and ratings depended on how well individuals performed on the task. Afterward, additional exploratory analyses were conducted to examine group differences in discrepancy scores between prediction scores (Anticipatory Awareness) and actual performance. The procedure was also completed for evaluation scores (Emergent Awareness). This method has been used to examine the Dunning-Kruger effect to examine if low performers are worse at predicting performance than high performers (Dunning, Johnson, Ehrlinger, & Kruger, 2003; Kruger & Dunning, 1999). Given the exploratory nature of this analysis only differences between the bottom and top tertiles were explored to reduce the number of comparisons made.



**Figure 14.** Performance Prediction and Evaluation Ratings and Actual Performance.

*NAB Judgment.* The results revealed a two-way interaction between score and group,  $F(4, 104) = 15.7, p < .001$ , with main effects for tertile group,  $F(2, 52) = 18.41, p < .001$  and report type  $F(2, 104) = 28.74, p < .001$ . Analyses of discrepancies between actual performance and ratings revealed significant differences in prediction discrepancies, (Top  $M=15.22, SD=22$ ; Bottom  $M=-34.6, SD=25.1$ ),  $t(34)=6.32, p < .001$  and evaluation discrepancies, (Top  $M=22.6, SD=19.9$ ; Bottom  $M=-37.37, SD=28.1$ )  $t(34)=7.381, p < .001$  between top and bottom groups. The top-performing group underestimated their performance while the bottom group overestimated performance (See Figure 15). There were no differences in predictor variable scores between the top and bottom groups.

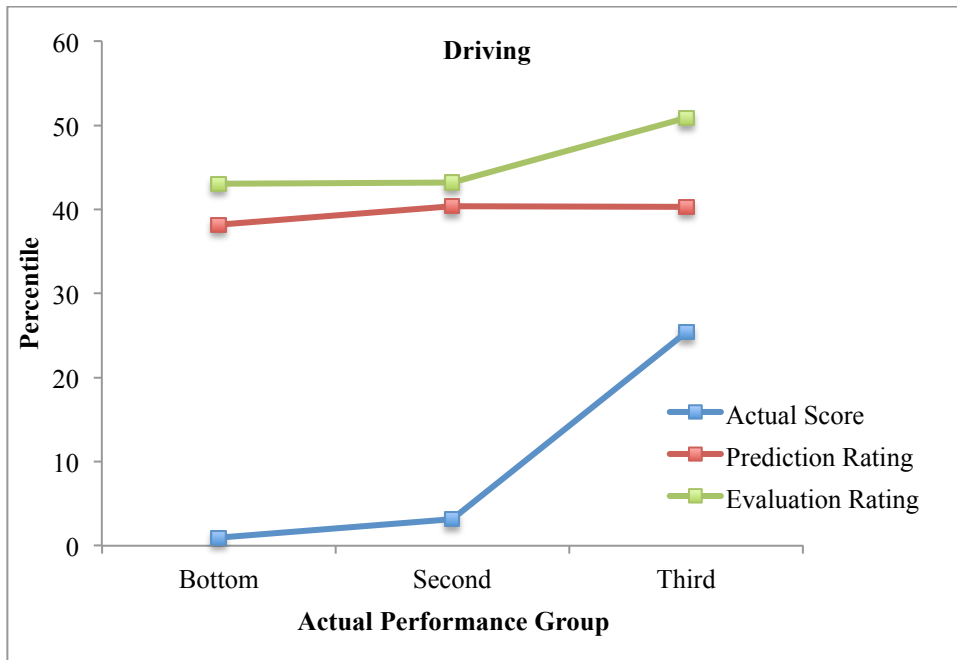


**Figure 15.** Patient ratings of Judgment and actual performance by tertile group based on actual performance.

*NAB Driving.* The results revealed a two-way interaction between score and group,  $F(4, 102) = 3.12, p < .05$ , with main effects for tertile group,  $F(2, 51) = 4.28, p < .05$  and score  $F(2, 102) = 72.23, p < .001$ .

There were significant differences between the top and bottom performing groups for both prediction discrepancies  $t(39) = 2.82, p < .01$  and evaluation discrepancies  $t(39) = 2.32, p < .05$ . Both groups overestimated their performance, but there were larger discrepancies between patient ratings and their actual performance for the lowest performers compared with the top performers (Prediction Means: Top  $M = -14.9, SD = 28.1$ ; Bottom  $M = -37.2, SD = 22.7$ ) (Evaluation Means: Top  $M = -25.47, SD = 19.8$ ) (See Figure 16). When examining mean group differences between top and bottom performers, the top performers also had significantly better HVLT-R Recognition scores, (Top  $M = 8.89, SD = 2.4$ ; Bottom  $M = 5.14, SD = 2.23$ ),  $t(39) = 5.192, p < .001$ , TMT-B Standard Scores, (Top  $M = 37.6, SD = 12.9$ ; Bottom  $M = 21.74, SD = 11.28$ ),  $t(39) = 4.2, p < .001$ , Unstructured Task Scores, (Top  $M = -1, SD = .78$ ; Bottom  $M = -1.8, SD = .53$ ),  $t(39) = 3.9, p < .001$ , and significantly lower Apathy (AES-C), (Top  $M = 42.2, SD = 12.75$ ; Bottom  $M = 50.64, SD = 7.4$ ),  $t(39) = 2.32, p < .05$ .

*NAB Immediate Memory Medications.* The results revealed a two-way interaction between score and group,  $F(4, 102) = 6.88, p < .001$ , with main effects for tertile group,  $F(2, 51) = 12.97, p < .001$  and score  $F(2, 102) = 21.7, p < .001$ . However, there were no significant differences in performance prediction or evaluation discrepancy scores between the top and bottom performing groups.



**Figure 16.** Patient ratings of Driving and actual performance by tertile group based on actual performance.

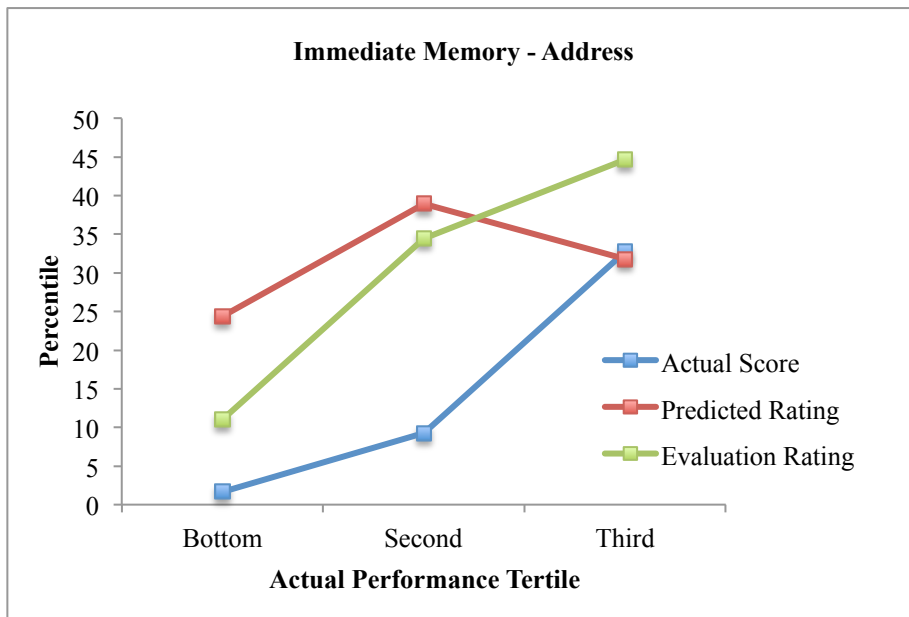
*NAB Delay Memory Medications.* The mixed model analysis did not reveal any interaction effects. There were main effects for tertile group,  $F(2, 51)= 12.39, p<.001$  and score  $F(2, 102)=21, p<.001$ . There were no significant differences between the lower and upper tertile groups for prediction or evaluation discrepancy scores of delay memory for medications.

*NAB Recognition Memory Medications.* The mixed model analysis did not reveal any interaction effects. There were main effects for tertile group,  $F(2, 52)= 11.14, p<.001$  and score  $F(2, 104)=42.85, p<.001$ .

There was no significant difference in tertile groups for prediction or evaluation discrepancy ratings of recognition memory for medications.

*NAB Immediate Memory Address.* The results revealed a two-way interaction between score and group,  $F(4, 104) = 6.38, p < .001$ , with main effects for tertile group,  $F(2, 51) = 14.25, p < .001$  and score  $F(2, 104) = 19.76, p < .001$ .

There was a difference in discrepancy scores for prediction of immediate memory (address) between top ( $M = -6.9, SD = 18.2$ ) and bottom performing groups ( $M = -10.5, SD = 16.3$ ),  $t(33) = 2.74, p < .01$  with a larger overestimations of performance by the bottom performing group (See Figure 17). There was no significant difference for evaluation discrepancies. Regarding differences in predictors between the top and bottom groups, there top group had significantly better performance on TMT-B Standard Scores, (Top  $M = 35, SD = 9.8$ ; Bottom  $M = 21.3, SD = 15$ ),  $t(33) = 3.268, p < .01$ , HVLT-R Recognition scores, (Top  $M = 8.3, SD = 2.9$ ; Bottom  $M = 5.9, SD = 2.7$ ),  $t(33) = 2.5, p < .05$ , Stroop Interference, (Top  $M = 50.7, SD = 5$ ; Bottom  $M = 46.5, SD = 4.9$ ),  $t(33) = 2.49, p < .05$ , and Unstructured Task, (Top  $M = -1, SD = .77$ ; Bottom  $M = -1.7, SD = .68$ ),  $t(33) = 2.83, p < .01$ .



**Figure 17.** Patient ratings of Immediate Memory for Address and actual performance by tertile group based on actual performance.



*NAB Delay Memory Address.* The mixed model analysis did not reveal any interaction effects. There were main effects for tertile group,  $F(2, 51) = 31.88, p < .001$  and score  $F(2, 102) = 18.55, p < .001$ .

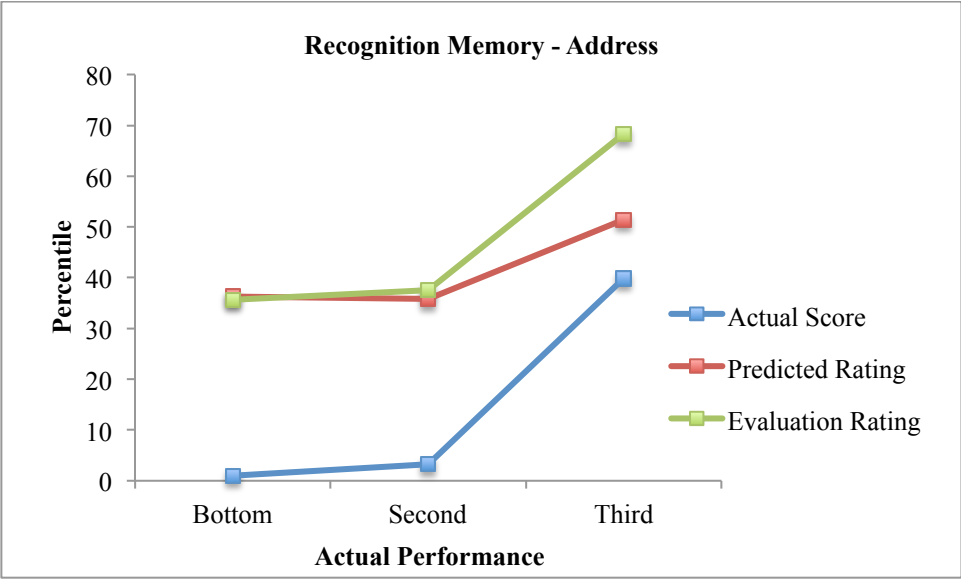
There were no differences in delay memory (address) prediction or evaluation discrepancies between the upper and lower tertile groups.

*NAB Recognition Memory Address.* The results revealed a two-way interaction between score and group,  $F(4, 104) = 2.61, p < .05$ , with main effects for tertile group,  $F(2, 52) = 17.79, p < .001$  and score  $F(2, 104) = 49.8, p < .001$ .

There was a significant difference in prediction discrepancies between top and bottom performing groups, with the bottom ( $M = -35.22, SD = 24$ ) group providing a larger overestimation of performance than the top group ( $M = -11.65, SD = 22.6$ ),  $t(36) = 3.1, p < .01$ . There was no difference in evaluation discrepancy scores (See Figure 18). There were also significant differences in predictor variables with the top performance group also performing better on the HVLT-R Recognition scores, (Top  $M = 9.4, SD = 1.8$ ; Bottom  $M = 5.2, SD = 3.2$ ),  $t(36) = 5.12, p < .001$ , TMT-B Standard Score, (Top  $M = 35.5, SD = 13.2$ ; Bottom  $M = 20.2, SD = 10.4$ ),  $t(36) = 3.95, p < .001$ , and the Unstructured task, (Top  $M = -1, SD = .79$ ; Bottom  $M = -1.9, SD = .46$ ),  $t(36) = 4.05, p < .001$ .

### **Exploratory Analysis: Metacognitive Knowledge and Online Awareness**

There were no relationships between Metacognitive Knowledge discrepancy scores (FrSBe and EMQ-R) and Online Awareness discrepancy scores.



**Figure 18.** Patient ratings of Recognition Memory for Address and actual performance by tertile group based on actual performance.

## **CHAPTER FOUR:**

### **DISCUSSION**

The purpose of this study was to explore cognitive (i.e. Executive Functioning and Memory) and emotional factors (i.e. Apathy) and their relationships with Metacognitive Knowledge and Online Awareness in symptomatic HD. *Metacognitive Awareness* of Apathy, Executive Dysfunction, and Memory and *Online Awareness* of Executive Dysfunction and Memory were specifically examined. This was an exploratory study; there have been no other studies to date that examined factors that may be associated with the development of unawareness in Huntington's disease. It was also unclear from previous research if unawareness, or anosognosia, is global or domain-specific in this population. It is also the first known study in HD to examine Online Awareness using a performance prediction and evaluation technique in addition to self/informant report discrepancies to study Metacognitive Knowledge.

#### **Metacognitive Knowledge in HD**

Metacognitive Knowledge is the overall beliefs about one's own abilities or self (Toglia & Kirk, 2000). Metacognitive Knowledge of Apathy, Executive Dysfunction, and Memory was measured with discrepancies between patient and informant report in these domains. It was hypothesized that Apathy, Executive Functioning, and Memory would independently be related

to Metacognitive Knowledge. Apathy and Executive Functioning would be more strongly related to Metacognitive Knowledge than Memory (Hypothesis One).

The proposed analysis to test this hypothesis was to use a multivariate multiple regression approach to examine these relationships. Initial simple correlational analyses of the Metacognitive Knowledge difference score outcome variables and the predictor variables revealed some relationships including Metacognitive Knowledge of Apathy and self-monitoring (Unstructured Task) and inhibition (Stroop Interference) as well as a relationship between Metacognitive Knowledge of Executive Dysfunction and inhibition (Stroop Interference). Graphical exploration of these findings indicated that a few participants' scores drove the Stroop relationships, so it may not be appropriate to draw conclusions about these relationships. The relationship between Metacognitive Knowledge of Apathy and the Unstructured Task score suggests that initially, as performance on the Unstructured Task improves, informants and patients are in better agreement. However, scores between the patients and informants tend to diverge as the Unstructured task score continues to improve, with the patients rating their Apathy more severely than the informants. This provides some evidence that executive functioning is associated with Metacognitive Knowledge and partially supports the hypothesis that this cognitive function is associated with awareness in HD.

### **Is Metacognitive Knowledge Domain Specific?**

It appears that the regression statistic was underpowered as several variables that were not significant in the simple correlational analyses became significant in the regression, indicating possible suppressor effects. Additionally, the use of difference scores in the regression caused the results to be even more difficult to interpret (as explained in the results section of this

paper). Therefore, further exploratory analyses were conducted to further examine the hypotheses.

When examining overall group means, informants provided higher ratings of Apathy than patients, however, there were no differences between patient and informant ratings of Executive Dysfunction and Memory. Notably, the HD patients on average rated their own Apathy and Executive Dysfunction above clinical cut-offs, suggesting they may have some awareness of these issues. No clinical cut-offs for the EMQ-R exist, so this could not be explored.

Further analysis was conducted to determine if group differences appeared when examining discrepancies between patient and informant report based on informant-rated symptom severity. Patients with the lowest informant-rated Apathy were in agreement with the informants, while those with the highest informant-rated Apathy underestimated their ratings compared to their informants. For Memory and Executive Dysfunction, the bottom tertile patient group rated their cognitive problems as more significant than their informants. Only for those with the highest informant-rated memory problems and executive dysfunction were the patient ratings lower than informant ratings. This suggests that these patients underestimated their cognitive issues compared to the informants. Overall, the results indicated that those with the most Apathy and Executive Dysfunction, and Memory problems according to informants were most unaware of their symptoms, supporting the hypothesis that there is an association with worsening apathy, memory and executive functioning and Metacognitive Knowledge.

To further explore the hypothesis that apathy, executive functioning and memory would be associated with Metacognitive Knowledge, comparisons were made between the top and bottom tertile groups since it was established that patients in the top tertile group underestimated their problems while those in the bottom group either agreed with their informant or

overestimated their problems. When comparing mean predictor variables between these groups, those who were most unaware of their Apathy also had the lowest scores on the Stroop Interference and TMT-B (both executive functioning tasks) and highest AES-C score (indicating more severe clinician-rated Apathy). Similarly, when comparing groups based on informant Executive Dysfunction ratings, there were differences between the highest and lowest groups for the executive functioning and clinician-rated apathy measure. Finally, when comparing groups based on informant memory ratings, there were significant differences in clinician-rated Apathy and Stroop scores. These results provide more evidence that Executive Functioning and Apathy may be associated with Metacognitive Knowledge in HD, while there is less evidence for the relationship between Memory and Metacognitive Knowledge.

A caveat of using the informants as the standard to create the tertile groups is that this may not be an accurate method to measure unawareness. There were almost no differences in ratings of apathy, executive functioning, among the patient tertile groups. While this may be because the patients are unaware, it may also be because of an unrelated, statistical problem. When creating groups based on informant scores, the informant scores may have more of a range between tertile groups than the patients. Therefore for the highest and lowest informant-rated groups, statistically, patients will most always overestimate compared to informants when informants are rating them low and underestimate when informants are rating themselves higher.

Because of this caveat, the same analyses were conducted by splitting the sample into groups based on MoCA score severity, as the MoCA provides an indication of overall cognitive dysfunction. Again, patients with the least overall cognitive impairment were in agreement with informants on their Apathy ratings, however, those with more cognitive impairment underestimated the severity of their Apathy relative to the informants. Patients and informants

were in agreement across severity groups for Executive Dysfunction and Memory scores. Perhaps this suggests that overall cognitive dysfunction is not enough to produce unawareness and there are specific domains of cognitive dysfunction that may be more predictive of the development of unawareness.

The results support other research that has proposed that self-monitoring is an avenue through which failures are recognized and is thus important for awareness. Executive functioning may also impact memory, which can then impact awareness, as executive functioning is required for the retrieval of relevant autobiographical memories (Morris & Mograbi, 2013; Robertson, 2010). Performance on the Unstructured task and Stroop test have been shown to associated with ventromedial prefrontal cortex activity, an area of the brain also associated with self-reflection, evaluation, recollection inhibition and self-monitoring (Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000; Potenza et al., 2003; Robinson et al., 2014). The findings are consistent with studies that suggest that awareness is associated with the ability to detect errors, which may explain HD difficulty providing accurate ratings as HD patients have been shown to have reduced error processing (Beste et al., 2006; Clare, 2002; Hannesdottir Metacognitive & Morris, 2007). The results also support the theory that apathy may be associated with Knowledge, as emotion tags significance or relevance to events, which is important in the ability to recognize failures.

### **Patient and Informant Report Compared with Objective Cognitive Measures**

The relationship between patient and informant report and the patients' actual cognitive functioning was also examined. While not directly testing the hypotheses, this analysis was important to determine if awareness is domain specific and also allowed the exploration of Metacognitive Knowledge with objective, cognitive measures. The HD patients' report of

Memory was correlated with performance on memory measures while only informant report of Executive Dysfunction was associated with performance on executive functioning measures. Similarly, informant Apathy ratings were associated with executive functioning task performance, while patient ratings were not. This suggests that HD patients may have a better appreciation of their memory functioning versus their Executive Dysfunction and Apathy. Also, as a group, the HD patients may be more aware of changes in memory than informants.

There are several possible explanations for these results. According to research of the Dunning-Kruger effect, those who are most unskilled in a particular ability are the least able to evaluate their ability in that skill (Dunning et al., 2003; Kruger & Dunning, 1999). Given research that has shown significant executive functioning deficits and increased apathy in HD, HD patients may not be able to evaluate themselves in these domains because they suffer from deficits in the domains. In contrast, past research suggests a relative sparing of memory functioning in HD compared to other neurodegenerative disorders, particularly Alzheimer's disease (Fine et al., 2008). In HD, memory problems are characterized by memory retrieval deficits, with relative sparing of memory retention (Massman, Delis, Butters, Levin, & Salmon, 1990). Because memory retention is spared in HD, HD patients may be better equipped to evaluate their functioning within this domain. Differences in anosognosia of memory have been shown across neurodegenerative disorders depending on the severity of memory impairment associated with the disorder. For example, while both AD and vascular dementia patients demonstrate worse awareness of memory than controls, vascular dementia patients had a better awareness of their memory abilities than AD patients (Morris et al., 2014). Research has shown that vascular dementia patients have less memory impairment than AD patients (Looi & Sachdev, 1999), which may explain the difference in awareness for memory impairment between



groups. It is possible that memory may not contribute to Metacognitive Knowledge in HD, except for those who are in most advanced stages of the disease when overall brain functioning declines. This supports the hypothesis that problems with executive functioning and apathy may be particularly important for the development of unawareness in HD.

Another explanation is perhaps informants do not detect subtle memory changes that patients may notice themselves. Hannesdottir and Morris (2007) proposed that self-report relies on a person's ability to review accumulated information that was gathered over a period of time. This would also be true for the informants. In a study comparing MCI and older healthy controls' awareness of memory abilities, the MCI group was more accurate than the control group in their self-ratings of verbal memory, which suggests that those experiencing "preclinical" memory impairment are more accurate in evaluating memory than controls (Cook & Marsiske, 2006). This is consistent with findings in the current study, in that those with relatively more subtle changes in memory reported more concerns with memory than the informants.

Another explanation may be about general beliefs and attitudes towards memory. Studies suggest that in the general population, there exist stereotypes about poor memory in aging individuals (Levy, 2003). Furthermore, some suggest that laypeople may not be able to distinguish among cognitive domains. Schoo, van Zandvoort, Biessels, Kappelle, and Postma (2013) suggested that individuals might mistakenly believe they have memory problems, when in fact, their memory failure may actually arise from executive functioning deficits rather than true memory impairment. Because Executive Dysfunction may impact memory in HD, such as the failure to use semantic clustering for example (Fine et al., 2008), HD patients may falsely believe their Executive Dysfunction is actually memory impairment, which may be why the patients are underreporting Executive Dysfunction. This may indicate that HD patients are aware

of their cognitive deficits, but they are wrongly attributing their executive dysfunction to memory problems. Further research may be conducted in different groups to determine if this pattern of better awareness of memory is specific to HD or if this is a phenomenon that other groups experience.

### **Metacognitive Knowledge and Caregiver Burden, Demographic Characteristics, and Disease Progression**

**Caregiver Burden.** The inclusion of a measure of caregiver burden in this study was an attempt to control for a potential bias in the informants' reports. Caregiver burden was negatively associated with Metacognitive Knowledge of Apathy suggesting that the informants who provided more severe ratings than the patients were also experiencing the most caregiver burden. This could mean that unawareness may cause informants to experience more burden, or that more burdened informants are likely to rate patients' symptoms more harshly. A recent study has shown that anosognosia is associated with increased use of support services, increased cost to the family, and total number of hours of informal care provided by relatives, regardless of dementia severity (Turró-Garriga et al., 2016), providing some support that anosognosia is associated with increased burden for the family system.

**Gender.** Gender was associated with Metacognitive Knowledge of Apathy; males were less aware of their own Apathy than females. In Parkinson's disease (PD), one study demonstrated an interaction between age and gender, where men were more apathetic in the older PD patient group and females were more apathetic in the younger PD patient group (Meyer et al., 2015). Further investigation into the relationship may be explored, as there is little research examining gender effects in anosognosia.

**Age.** Age was also negatively associated with Metacognitive Knowledge of Executive Dysfunction and Memory, suggesting younger patients were more aware of their symptoms than older patients.

**Education.** There were no relationships between Metacognitive Knowledge variables and education.

**Motor Scores.** Metacognitive Knowledge of Apathy and Executive Dysfunction were negatively associated with motor symptom severity, providing some evidence that disease progression is associated with Metacognitive Knowledge.

### **Metacognitive Knowledge Conclusions**

Results partially support the hypotheses; Executive Functioning, specifically inhibition and self-monitoring, was the most prominent cognitive variable associated with Metacognitive Knowledge in HD in simple correlational analyses. Executive functioning is thought to contribute to the overall sense of self and allows one to update self-identity when new information is presented or when failures occur (Morris & Mograbi, 2013). This is consistent with past research that shows HD is associated with significant executive functioning decline (Paulsen, 2011). There is also some evidence that Apathy is associated with Metacognitive Knowledge in HD in exploratory analyses examining differences between patient groups with larger or smaller discrepancy ratings with their informants. There is not enough evidence in this study to show that decline in memory is associated with Metacognitive Knowledge in HD.

Regarding specific domains of Metacognitive Knowledge, patients who were most severely impaired in a domain tended to be most unaware of symptoms, regardless of domain. This is consistent with past research that suggests that agreement between patient and informant

on measures of frontally mediated behaviors tends to worsen with overall disease progression (Hergert (Blinkoff), Sanchez-Ramos, & Cimino, 2015). The results also suggest that awareness may be domain specific in HD. HD patients may have better Metacognitive Knowledge of their Memory than Executive functioning and Apathy. This supports past research that has demonstrated prominent executive functioning deficits and increased apathy with relatively spared memory in HD (Paulsen, 2011) and that those who have more deficits in a specific domain tend to be most unaware of their abilities in that domain (Dunning et al., 2003).

### **Online Awareness**

Online awareness is activated within a specific situation and involves judgments of abilities related to that specific situation. According to the Toglia and Kirk model of awareness, Anticipatory Online Awareness is the appraisal of a current situation, while Emergent Online Awareness is associated with self-monitoring or self-evaluation during a task (Toglia & Kirk, 2000). Online Awareness of Executive Functioning and Memory was explored through discrepancies between actual performance on tasks found in everyday living and prediction (Anticipatory Awareness) and evaluation (Emergent Awareness) ratings of performance. Larger discrepancy scores indicated lower ability to predict or evaluate performance. This study used a rating approach in which patients were asked to compare their performance to healthy individuals without HD with similar, age, gender and education by providing a percentile rating (Rosen et al., 2010; Williamson et al., 2010). It was hypothesized that Apathy, Executive Functioning, and Memory would be independently associated with Anticipatory (Hypothesis Two) and Emergent Awareness (Hypothesis Three) of Executive Functioning and Memory and

that Apathy and Executive Functioning would be more strongly related to Online Awareness than Memory.

### **Is Online Awareness Domain Specific?**

Similarly to the Metacognitive Knowledge analysis, the proposed analysis to test these hypotheses was to use a multivariate multiple regression approach to examine these relationships. Initial correlational analyses, however, did not indicate any convincing relationships among the predictor and outcome variables. The multivariate multiple regression was underpowered and suppression effects also arose, making the regression analysis difficult to interpret. Therefore, exploratory analyses were conducted to further examine Online Awareness.

For the whole sample, mean performance prediction (Anticipatory Awareness) and evaluation (Emergent Awareness) ratings were significantly higher than actual performance for all NAB Daily Living tasks. While not a test of the hypotheses, this finding could have significant implications for daily functioning and safety, as this could mean HD patients may overestimate their abilities in similar everyday tasks, such as taking their medications and driving. It also supports past research that HD patients tend to overestimate their performance on activities of daily living compared to informant report (Hoth et al., 2007). As a group, overall predictions and evaluations of memory performance were correlated with actual memory performance while this was not true of the relationships between executive function predictions and evaluations and actual performance. Similar to the Metacognitive Knowledge that suggested that HD patients have a better awareness of memory than executive functioning, these results also suggest that HD patients may have a better Online Awareness of memory than executive functioning.

In examining possible differences between those who are more unaware versus aware, those who performed the worst on each NAB task had the largest discrepancies between actual performance and prediction and evaluation ratings, suggesting that they had the poorest Online Awareness. This is consistent with the other studies that have demonstrated the Dunning-Kruger effect. In healthy populations, top performers tend to provide the best estimates of their performance compared to the poorer performers. Those who perform the worst on tasks tend to overestimate actual level of performance. The effect has shown that the poorer the competency in a domain, the larger discrepancy in the estimation that is given by the performer in that domain (Kruger & Dunning, 1999, 2009; Schoo et al., 2013). This effect has been demonstrated in several domains in healthy individuals, including on college exams, and expertise in professional domains, such as medical technicians knowledge of medical terminology (Dunning et al., 2003; Ehrlinger, Johnson, Banner, Dunning, & Kruger, 2008). The theory proposes that the cognitive mechanisms required to do well on those tasks are the same mechanisms required to estimate performance (Dunning et al., 2003). In this study, those who performed poorly on the Daily Living Memory NAB tasks, likely have impairments in learning, storage, free recall, and/or recognition of verbal information. NAB Judgment performance is associated with deficits in problem-solving or poor knowledge of home or health safety issues. NAB Driving difficulty may indicate issues with visuospatial working memory, visual scanning, and attention (Stern & White, 2003). These cognitive abilities are also associated with the inability to update new information about the self according to the CAM model (Morris & Mograbi, 2013), which may explain why poor performers on these tasks also had the worst Online Awareness. To relate these findings to the hypothesis that executive functioning and memory would be related to online

awareness, perhaps cognitive deficits, as shown by poor performance on those specific NAB tasks, contribute to an inability to predict or evaluate performance on the task.

In an attempt to test the hypothesis that apathy, executive functioning, and memory would be associated with online awareness, differences in the predictor variables between those who were most aware and least aware were explored. Those with the best Online Awareness tended to perform better on executive functioning and memory predictor variables, as well as having overall lower clinician-rated Apathy. While these analyses do not control for other factors and do not establish the independent contributions of these variables, these analyses do provide some support for the hypothesis that Apathy, Executive Functioning, and Memory are associated with Online Awareness in HD.

Another explanation is that people have difficulty assessing their own abilities in general. People tend to overestimate or are highly optimistic about their abilities. Research has shown that people tend to estimate their abilities as “above average” (Lovallo & Kahneman, 2003; Dunning, Heath & Suls, 2004). This is statically impossible, in that there is variation in ability among the population. In examining these results, this should be taken into consideration, as regression effects would make it so people who are the best performers would almost always underestimate their performance while the worst performers would almost always overestimation their performance and that those who are further away from the mean would be more discrepant. There does appear to be a difference, however, in discrepancies between ratings between best and worst performers, suggesting that the top performers were more accurate in their ratings than bottom performers.

## **Online Awareness and Relationships with Disease Progression and Demographic Characteristics**

**Motor Scores.** Motor scores were not associated with Online Awareness variables.

**Education.** There was no relationship between education and Online Awareness variables.

**Age.** Age was positively associated with Anticipatory Awareness of Recognition Memory and Delayed Memory evaluation suggesting that the older people were more accurate in their predictions and evaluations of memory. One explanation may be stereotypes of the relationship between cognition and age. Furthermore, it is notable that younger age of symptom onset in HD is associated with a more rapid onset of symptoms (Foroud, Gray, Ivashina, & Conneally, 1999) (Walker, 2007). According to the Toglia and Kirk model, culture and context can influence online awareness (Toglia & Kirk, 2000). Studies have shown that individuals have beliefs that their own memory will decline as they age (Clare, 2002; Levy, 2003; Ryan & See, 1993).

## **Online Awareness Conclusions**

Overall, HD patients tend to overestimate their performance on Executive Functioning and Memory tasks, especially those who perform the poorest on these tasks. There is also some evidence that as a group, patients are better at predicting and evaluating memory performance than executive functioning, which is similar to findings that Metacognitive Knowledge for memory is better than executive functioning. This suggests that awareness in HD is governed by local monitoring systems rather than a single metacognitive mechanism. When comparing those with the best Online Awareness to those with the worst, those with the smallest discrepancies



between performance and ratings also performed the best on measures of Memory, Executive Functioning, and had the lowest Apathy, supporting the hypothesis that these factors are related to Online Awareness and is consistent with past research that indicates apathy, executive functioning, and memory are important cognitive contributors to awareness.

### **Psychological Explanations for the Results**

Another explanation for the results is that HD patients are experiencing denial and not anosognosia. Prigatano (2014) proposed that with true unawareness, there is a lack of self-perceived issues, while with true denial, there is an unrealistic perception of self. Both of these processes can co-occur. Some suggest that denial can be distinguished from anosognosia in the emotional reaction that is displayed by the person following feedback of their performance or functioning. A negative reaction is associated with denial, while a perplexed reaction is related to anosognosia. It is also suggested that avoidance is a coping behavior associated with denial (Kortte, Wegener, & Chwalisz, 2003; Toglia & Kirk, 2000). In this study, participants were not provided feedback of results, so it may be difficult to determine which aspects of these results are related to denial versus anosognosia. Denial and/or unawareness may also occur for family members for similar reasons (Clare, 2002), which is important to consider given that informant report was used to measure Metacognitive Knowledge.

Psychological factors may also promote unawareness as a protective strategy to enhance well-being, particularly when there is a perception of loss of control or independence (Clare, 2002). Therefore, there may be some positive aspect of being unaware of symptoms. Social psychology research suggests that healthy individuals selectively attend to information that confirms their biases and expectations. This especially occurs when a person becomes ill or

disabled or when a person is exposed to disconfirming feedback of his or her concept of self because the self-concept is under threat with the onset of illness. Therefore, minimizing can be used as a strategy to cope (Clare, 2002). In fact, several studies suggest that anosognosia is inversely related to depression, suggesting anosognosia may provide some protection against low mood (Conde-Sala et al., 2013; Kashiwa et al., 2005).

Furthermore, Toglia & Kirk (2000) suggested that errors are more difficult to recognize when the task is more highly valued and more related to self-identity. For example, for patients with traumatic brain injury, performance related to IADLs is frequently overestimated, which may be because these tasks are associated with personal control (Toglia & Kirk, 2000). The NAB Judgment task can be seen as a representation of independence since it asks patients safety related questions. If the patient demonstrates that he or she has a deficient knowledge of being safe, his or her independence may be threatened. While not an actual driving task, the NAB Driving task may be in a similar category because driving also represents independence. In fact, epidemiologic studies suggest that driving cessation in older adults is associated with increased depression (Breen, Breen, Moore, Breen, & O Neill, 2007; Ragland, Satariano, & MacLeod, 2005). Since independence is valued by individuals in general (Ball et al., 2004) it may be more difficult for the patients to detect or admit to errors in these tasks.

## **Study Limitations and Future Directions**

### **Relationships between Metacognitive Knowledge and Online Awareness**

Toglia and Kirk (2000) described the relationship between Metacognitive Knowledge and Online Awareness as a dynamic process, whereby each type of awareness can influence the

other. This is consistent with the idea that individuals use a “top-down” approach when estimating performance. That is, individuals begin with an overall belief of their skill and then use the belief to estimate how they will do on the specific task (Dunning et al., 2003). For example, individuals may be unaware of their symptoms when they are questioned about them, but are aware when faced with a task and confronted by their disability (Hannesdottir & Morris, 2007; Moro, Scandola, Bulgarelli, Avesani, & Fotopoulou, 2014). This suggests that one type of awareness may be intact, while the other is not. Further research could examine the relationship between Metacognitive Knowledge and Online Awareness in HD.

### **Addressing Denial versus Anosognosia**

Future studies should include a survey asking patients why they selected the rating that they did to gain a better understanding of their ratings. For example, it was not explored if the participant truly thought he or she did well on the task or if there was there some fear of consequences of doing poorly on the tasks. Future studies may provide feedback and code how patients react to determine if they are experiencing denial or true unawareness.

### **Use of a Comparison Group**

**Control Group.** This study did not use control participants so it may be difficult to determine whether or not people, in general, have a difficult time predicting and evaluating performance. Some suggest that even healthy individuals have difficulty predicting and evaluating performance (Furnham, 2001), so including controls may help to understand if there are relative differences in awareness compared to HD. While this may raise the question if anosognosia is pathological, it does seem that it can be particularly detrimental in

neurodegenerative populations like HD given possible safety concerns that may arise due to overestimation of abilities.

**Alzheimer's Disease.** It may also be worthwhile to complete this study comparing Huntington's disease with Alzheimer's disease patients, given that memory is impaired while executive functioning is relatively spared in AD. It would be interesting to see if differences in anosognosia emerged when directly comparing these populations. For example, AD patients may show more mnemonic anosognosia than the HD patients. This could demonstrate how deficits in different cognitive functions may cause anosognosia to develop in specific domains.

### **Additional Factors**

There are many other factors that may be associated with awareness in Huntington's disease, such as personality and other psychiatric factors (e.g. anxiety, depression). Future research may investigate these factors in relationship to unawareness in this population. Additionally, including different cognitive tasks in domains not theorized to be related to awareness, such as in language or visuospatial abilities, may be used to demonstrate that memory and executive dysfunction are specifically related to awareness and not overall cognition decline.

Forty-eight percent of the sample was on anti-chorea/antipsychotic medications to manage chorea. These medications affect the dopamine system, which may influence the expression of frontally-mediated behaviors such as apathy and executive dysfunction or even the expression of awareness (Hergert (Blinkoff) et al., 2015). It may be beneficial to examine results with a sample of patients who are not taking medications for chorea.

Recent work suggests that despite overestimations in ratings, the most unskilled also are least confident in their ratings (Miller & Geraci, 2011). While confidence in ratings was not

explored in this study, the technique has been used in AD. In one study, those rated were rated as unaware did not change confidence ratings when given the chance to rate performance retrospectively (Cosentino et al., 2016). Confidence in rating is another way of examining awareness and may be further explored in future studies.

### **Methods Limitations**

**Statistical Power.** While regression was intended to best test the hypotheses, given the rarity of HD, a larger number of HD patient and informant pairs could not be recruited. Some effects may be small and a larger sample may have been necessary to detect those effects. All eligible patients who were in the USF HD Registry, which includes patients who live in the entire state of Florida, were approached to participate. Perhaps a multisite study across states would be necessary to achieve the numbers needed for sufficient power to detect what could be small effects in a multivariate regression framework.

**Patient Past Exposure to Neuropsychological Testing.** Many of the patients have been exposed to neuropsychological testing, especially since a large portion of the patients in this study was recruited from other research studies. While the NAB is not part of the UHDRS test battery typically used in HD studies, perhaps being exposed to neuropsychological tasks may skew the results of the performance prediction and evaluation portion of the study if the patients have gotten feedback on their performance on similar testing in the past.

**The AES-C.** There were several issues with the use of the AES-C as a measure of clinician-rated Apathy. The intent was to have a more objective measure of Apathy to serve as a predictor variable. As outlined in the introduction, clinician-rated scales are not completely unbiased. Also, clinicians are only seeing the patient at one point in time, so they may not get an

overall view of the person's actual functioning on a daily basis. The AES-C was based on the patients' behaviors and responses, so scores may be more reflective of the patient's perception of Apathy. Coding of the patients' responses was also challenging in that they often provided yes/no answers even with prompts or just used the rating terms used by the questionnaire (e.g. slightly characteristic, somewhat characteristic).

The administrator of the AES-C was also not blinded to the study's hypotheses. The AES-C requires at least a bachelor's level clinician. It is suggested that this clinician has at least two years experience within psychological clinical settings (Clarke et al., 2007). The primary experimenter was the only study staff member who met these requirements and was available when each participant's study session occurred. This could lead to potential bias in the results of this measure and there should be some caution in interpreting the results of this measure. However, this is a preliminary study and results may represent at least a proof of concept that can be replicated in a study with more staff available.

There were no relationships between the AES-C and outcome variables in simple correlational analyses, however, several relationships emerged with the AES-C variable within the regression analyses, indicating there may be a suppressor effect with this variable. Suppressor effects occur when a predictor has a significant effect in a regression, only when another variable is included and is held constant (Field, 2009). Therefore, results related to the AES-C should be interpreted cautiously in the regression analyses, as these effects may emerge from small sample sizes or being included with other predictors that are highly correlated (Thompson & Levine, 1997).

**EMQ-R.** There were no norms for the Everyday Memory Questionnaire – Revised for patients or informants so raw scores were used.

**Executive Functioning Tests.** The TMT and Unstructured task are written tests. Studies have shown a strong motor component for the TMT (Kortte, Horner, & Windham, 2002). Performance on these tasks may have been influenced by motor and processing speed in addition to possible executive function contribution. In future studies in HD, it would be important to consider the use other executive tasks that do not rely on motor functioning. Some examples include the Iowa Gambling Task, a test of decision-making or the Stockings of Cambridge task, a test of planning that has been suggested for use in HD clinical studies (Lezak et al., 2012; Stout et al., 2014).

## **Conclusions**

This research has a number of contributions and implications. This research provides insight into the possible contributors of unawareness in HD. It may also contribute to the development of a model of anosognosia for basal ganglia dysfunction. The study also provides support for using performance prediction and evaluation paradigms in HD for use in future studies. Executive Functioning, particularly inhibition and self-monitoring, appears to be related to Metacognitive Knowledge in HD, however, the study also provides some preliminary evidence that Apathy is also associated with Metacognitive Knowledge. The study also provided some evidence for an association between Online Awareness and Executive Functioning, Memory, and Apathy. Also, as a group, HD patients tend to overestimate their performance on tasks associated with daily functioning. This can have important safety implications for patient functioning in day-to-day life. For both Metacognitive Knowledge and Online Awareness, HD patients tended to have a better awareness of memory compared with executive functioning and apathy, suggesting awareness may be domain specific in this population and may be related to

the fact that HD patients tend to have significant executive dysfunction and apathy with relatively intact memory. Those with the most severe symptoms across domains, however, tended to be most unaware, while those with less severe symptoms tended to be more aware of their functioning. Because of this, clinicians should be aware that when gathering information, it is important to get perspective from the patient, as patients may have accurate information about themselves, particularly for those who are earlier in the disease progression. In contrast, it may be important to gather additional information independent of the patient's report for those whose disease is more advanced.



**CHAPTER FIVE:**  
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**APPENDIX A:**  
**PROCEDURE INFORMATION**

**Performance Prediction and Evaluation Scripts and Bell Curve**

“In a few moments we will start to do some tasks looking at your thinking abilities. I would like to know how well you think you will do on the task compared to other people similar to you. I want you to imagine that we gave the same task to 100 healthy people of the same gender, similar age and with similar levels of education (So imagine 100 men or women [depending on their gender] that are your age and has the same level of education WITHOUT HD). Imagine that we then lined them up, based on their scores from best (or highest) to lowest (or worst) [Show them the bell curve]. If we look at a group of 100 people, we see that very few people do really poorly [point to the low end of the graph], and very few people do extremely well [point to the high end of the graph], and most people fall here around the 50<sup>th</sup> percentile. *Ask if the participant has questions. These instructions can be repeated as much as necessary.* Additionally, at some points during the testing, I’m going to stop and ask you to tell me how you think you did on the test. When I ask you how you did, I’d like you to tell me how well you think you did on the test compared to other people similar to you.” **Ask if the participant has questions. These instructions can be repeated as much as necessary.**

The participant is then presented with the instructions as indicated by standard NAB test protocol. Before beginning the task, participants will be asked “Please tell me how you think you will perform on this task compared to healthy people like you: below average, average, or above average?” Record the participant’s response. Afterwards say, “Ok here the is the graph we looked at earlier [present bell curve]. Please point out where you would be on this graph.” After the task was completed say, “Please tell me if you think you performed below average, average, or above average.” Record the participant’s response. Afterwards say, “Ok here the is the graph we looked at earlier [present bell curve]. Please point out where you would be on this graph.”

**Table 1A.** Order of counterbalanced neuropsychological tasks.

Version 1	Version 2	Version 3	Version 4
1. HVLТ-R Immediate Trials 2. Stroop 3. TMT 4. NAB Judgment 5. NAB Driving 6. HVLТ-R Delay 7. NAB Everyday Memory Immediate 8. Unstructured Task 9. NAB Everyday Memory Delay	1. HVLТ-R Immediate Trials 2. Stroop 3. TMT 5. NAB Driving 6. NAB Judgment 6. HVLТ-R Delay 7. NAB Everyday Memory 8. Unstructured Immediate 8. Unstructured Task 9. Everyday Memory Delay	1. NAB Everyday Memory Immediate 2. Unstructured Task 3. Everyday Memory Delay 4. HVLТ-R Immediate Trials 5. Stroop 6. TMT 7. NAB Driving 8. NAB Judgment 9. HVLТ-R Delay	1. NAB Everyday Memory Immediate 2. Unstructured Task 3. Everyday Memory Delay 4. HVLТ-R Immediate Trials 5. Stroop 6. TMT 7. NAB Judgment 8. NAB Driving 9. HVLТ-R Delay



**APPENDIX B:**  
**INFORMANT DEMOGRAPHICS QUESTIONNAIRE**

**Subject #:** \_\_\_\_\_ **Years of Education:** \_\_\_\_\_

**Age:** \_\_\_\_\_ **Gender:** \_\_\_\_\_

**Ethnicity (circle one):**

Hispanic/Latino    Non-Hispanic or Latino    Ethnicity Unknown/Prefer not to answer

**Race (circle one or more):**

African-American/Black    Asian    American Indian/ Alaskan Native

Native Hawaiian/Pacific Islander    White    Race Unknown/Prefer not to answer

**What is your relation to the patient?** \_\_\_\_\_

**How well do you know the patient? (Circle one)**

Hardly At All    Not So Well    Fairly Well    Pretty Well    Very Well

**How long have you known the patient?** \_\_\_\_\_

**What is your HD status? (Circle one)**

Not at risk (no family history, unrelated to the patient)

At Risk (Family history, but have not had the gene test)

Gene Positive (had the gene test, but do not have symptoms of HD)

Gene Negative (had the gene test and do not have the HD gene)

**APPENDIX C:**  
**DESCRIPTIVE STATISTICS**

**Table 2A.** Patient Disease Characteristics: Main Variables of interest are bolded and have skewness and kurtosis listed.

	<i>N</i>	Sample's Score Range	Mean	<i>SD</i>	Skewness	Kurtosis
MoCA Raw	56	9 - 28	20.24	5.09		
MoCA z	56	-3.86-1.22	1.22	-.82		
<b>UHDRS Motor Score</b>	<b>56</b>	<b>3-65</b>	<b>29.98</b>	<b>16.77</b>	<b>.245(.319)</b>	<b>-1.01 (.63)</b>
Age Motor Sx Onset	52	23-63	44.88	10.51		
Age of Diagnosis	51	24-65	47.45	9.96		
CAG Repeat Larger Allele	44	40-57	43.5	2.88		
CAP Score	44	308.28-770.22	494.87	88.75	.549 (.36)	1.332 (.71)
<u>Chorea</u>						
<u>Medications:</u>	N					
None						
Risperidone	29					
Xenazine	19					
Haldol	1					
Olazapine	1					
Orap	4					
	2					

\*Indicates a significant deviation from normal at  $p < .05$ ; Variables used in main analyses are bolded

**Table 3A.** Descriptive Statistics of Predictor Variables Neuropsychological Measures & Apathy for the Sample.

	<i>N</i>	Score Range	Mean	<i>SD</i>	Skewness	Kurtosis
<b>Apathy Evaluation Scale Total Score</b>	<b>56</b>	<b>20-66</b>	<b>44.73</b>	<b>11.4</b>	<b>-.399 (.32)</b>	<b>-.56 (.63)</b>
<u>HVLT-R:</u>						
Immediate Total Raw	56	3-28	14.98	5.97		
Immediate Total T-score	56	20-49	25.89	8.71		
Delay Raw	56	0-11	3.9	3.36		
Delay T-score	56	20-55	27.27	10.54		
<b>Recognition Raw</b>	<b>56</b>	<b>-1 – 11</b>	<b>7.16</b>	<b>3.11</b>	<b>-.52 (.319)</b>	<b>-.63 (.63)</b>
<b>Recognition T-score</b>	<b>56</b>	<b>20-52</b>	<b>31.21</b>	<b>12.44</b>	<b>.485 (.319)</b>	<b>-1.5 (.63)*</b>
Percent Retention Raw	56	0-117%	56.18	38.83		
Percent Retention T-score	56	20-65	34.79	16.25		
<u>Trail Making Test:</u>						
Trails A Time Raw	53	18-180 sec	59.28	34.01		
Trails A T score		4-64	31.7	14.79		
Trails B Time Raw	53	36-300 sec	159.73	83.83		
Trails B T score	53	4-69	29.77	14.79		
<b>Trails B/A adjusted score</b>	<b>56</b>	<b>-6.1-1.52</b>	<b>-.99</b>	<b>1.82</b>	<b>-1 (.32)*</b>	<b>.732(.628)</b>
TMT-B-A adj score	56	-15.9-1.51	-4.18	4.22		
<u>Stroop Test:</u>						
Color-Word Raw	55	0-52	22.13	11.2		
Color-Word T score	55	15-60	33.66	9.76		
<b>Interference T score</b>	<b>56</b>	<b>31-64</b>	<b>48.9</b>	<b>6.02</b>	<b>.002 (.319)</b>	<b>.5 (.628)</b>
<u>Unstructured Task:</u>						
# High Value Completed	54	0-9	3.56	1.89		
# Low Value Completed	54	0-6	2	1.45		
# High Value Attempted	54	0-3	.57	.77		
# Low Value Attempted	54	0-2	.74	.71		
<b>Total Points Earned</b>	<b>54</b>	<b>5-450</b>	<b>197.44</b>	<b>104.96</b>	<b>-.03 (.325)</b>	<b>-.8 (.639)</b>
<b>Total Points Standard Score (Imputed)</b>	<b>56</b>	<b>-2.61-.67</b>	<b>-1.3</b>	<b>.75</b>	<b>.269 (.319)</b>	<b>-.65(.629)</b>

\*Indicates a significant deviation from normal at  $p < .05$ ; Variables used in main analyses are bolded

**Table 4A.** Descriptive Statistics of Main Variables – Metacognitive Knowledge Variables.

	<i>N</i>	Score Range	Mean	<i>SD</i>	Skewness	Kurtosis
<u>Everyday Memory:</u>						
Patient Report	56	0-52	24.26	15.74		
Informant Report	50	0-50	20.7	13.96		
<b>Discrepancy</b>	<b>50</b>	<b>-46-33</b>	<b>3.46</b>	<b>2.72</b>	<b>-.53 (.337)</b>	<b>-.44 (.662)</b>
<u>Apathy:</u>						
Patient Report	56	30-120 (T)	72.75	19.74		
Informant Report	50	44-136	87.96	19.36		
<b>Discrepancy</b>	<b>49</b>	<b>-56-30</b>	<b>-16.1</b>	<b>2.99</b>	<b>-.022(.337)</b>	<b>-.624(.662)</b>
<u>Executive Dysfunction:</u>						
Patient Report	56	37-119 (T)	75.45	17.32		
Informant Report	50	44-112	75.67	15.99		
<b>Discrepancy</b>	<b>49</b>	<b>-47-32</b>	<b>-1.9</b>	<b>2.75</b>	<b>-.633 (.33)</b>	<b>-.394(.662)</b>

\*Indicates a significant deviation from normal at  $p < .05$ ; Variables used in main analyses are bolded

**Table 5A.** Descriptive Statistics of Main Variables – Performance Prediction Evaluation

Variables

	<i>N</i>	Score Range	Mean	<i>SD</i>	Skewness	Kurtosis
Judgment Raw	55	9-19	13.75	2.49		
Judgment %ile	55	1-95%ile	34.58	28.95		
Prediction						
Discrepancy	55	-91-57	-16.92	32.39	.136 (.322)	-.45 (.634)
Evaluation	54	-91-56	-11.21	23.18	-.096 (.325)	-.41(.639)
Discrepancy						
Driving Raw	54	14-54	33.46	9.73		
Driving %ile	54	1-55	10.11	13.67		
Prediction	54	-84-22	-29.37	26.88	.244(.325)	-.829(.639)
Discrepancy						
Evaluation	54	-94-13	-35.76	23.18	-.099(.325)	.004(.639)
Discrepancy						
<u>Medication:</u>	55					
Immediate Raw		3-26	17.73	5.85		
%ile		1-75%ile	15.6	17.66		
Delay Raw		0-9	5.42	2.67		
%ile		1-75	13.36	17.29		
Recognition		0-2	.67	.72		
%ile		1-75	14.2	17.95		
<u>Address:</u>	55					
Total		2-22	13.47	4.89		
%ile		1-50	15.8	21.26		
Delay		0-8	3.18	2.55		
%ile		1-75	14.16	19.15		
Recognition		1-8	6	1.78		
%ile		1-75	14.2	17.95		

\*Indicates a significant deviation from normal at  $p < .05$ ; Variables used in main analyses are bolded

**APPENDIX D:**  
**GENERAL DATA DIAGNOSTICS**

**Missing Data**

All data were inspected for missing data points. Two participants did not complete the Unstructured Task and Trail Making Tests because they had difficulty writing due to problematic movements. One participant did not complete the Unstructured Task due to time limitations. One participant had some problems with vision and had difficulty completing the Trail Making and Stroop Tests. One participant is missing the NAB Driving task total score and evaluation score because the correct stimulus book was unavailable. That same participant person was missing delayed address memory prediction scores due to examiner error. One participant did not complete the performance prediction/evaluation part of the study because of time limitations. One participant is missing informant FrSBe scores due to informant error in completing the form. Forty-four participants had CAG genetic reports available. The rest of the participants (12) were diagnosed with HD based on a family history of HD and confirmation by neurologic exam.

Data imputation was considered to maximize the number of participants included in the analysis. Little's MCAR (Missing Completely at Random) test was conducted for the following variables: TMT-A and TMT-B total time and standard score, Unstructured Task total points, and Stroop Word, Color, Color-Word Time and Standard score as well as Stroop Interference, and the NAB driving total score and performance evaluation. Results of the analysis were non-

significant,  $\chi^2(24)=22.728$ ,  $p=.536$ , indicating that missing data is missing completely at random. Multiple imputation is appropriate. Five iterations were created with the MI approach in MPLUS. These data iterations were averaged and then the data was added to the original dataset.

### Variable Conversions and Calculations

For questionnaires and cognitive tests where normative data was available, raw scores were converted to standard scores. Table 15 indicates the normative corrections available for each measure (only measures with normative data are listed).

**Table 6A.** Normative data available for each measure.

	Age	Gender	Race/Ethnicity	Education
FrSBe	X	X		X
HVLT-R	X			
TMT	X	X	X	X
Stroop	X			X
NAB Tasks	X	X		X
Unstructured Task	X			

### Examining Normality and Outliers

Descriptive statistics and skewness and kurtosis were then calculated for all predictor and dependent variables. Data histograms for each variable were visually inspected to assess normality and to detect outliers. Additionally, guidelines by Field (2009) were used to determine deviations from normality by transforming skewness and kurtosis values for each variable into z-

scores. Any z-score of an absolute value greater than 1.96, was deemed as a significant deviation from a kurtosis and skewness of 0 ( $p < .05$ ), therefore indicating a violation of normality (see Table X in Appendix A). Because the HVLT – R Recognition standard score deviated significantly from normality because most patient’s standard scores were at floor ( $T < 20$ ), the HVLT-R Recognition Raw scores were used instead as these scores are distributed normally, and also seem to better capture the range of the participants’ recognition memory abilities.



## APPENDIX E:

### ADDITIONAL ANALYSES FOR METACOGNITIVE KNOWLEDGE

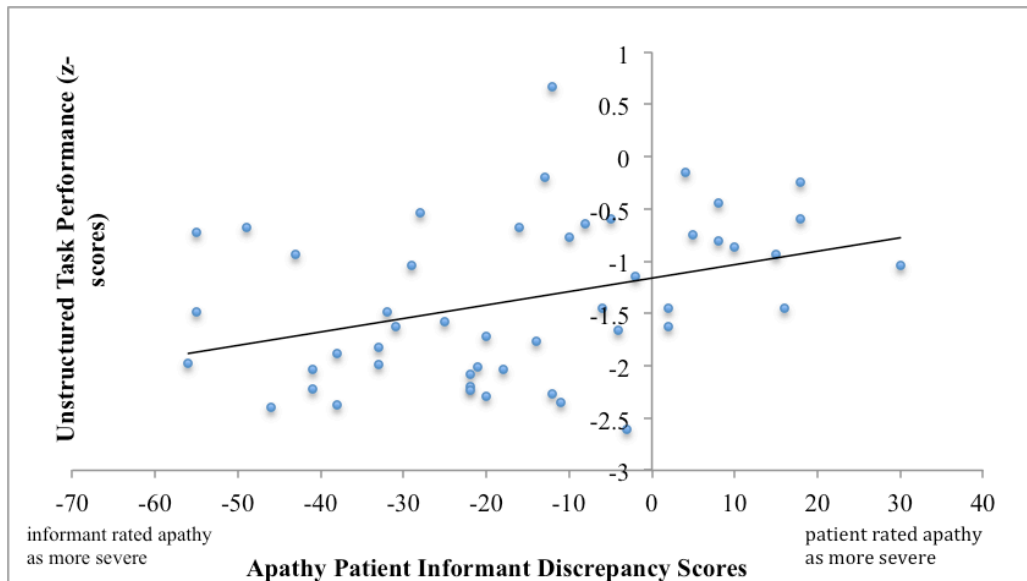
#### Correlations among Primary Predictors (“Objective” Measures) and Outcome Variables

Correlational analyses between the Metacognitive Knowledge discrepancy scores and the proposed main predictor variables (Unstructured Task Total Points standard score, TMT B/A Ratio Score, Stroop Interference score, AES-C total score, and the HVLT-R Recognition) were examined. Forty-eight participants were included in this analysis (2 were excluded because they were found to be influential data points in the main multivariate regression analysis, therefore the same participants were included in this analysis for consistency). Negative agreement scores indicate that the informant provided more severe ratings than the patient provided. The **Apathy** discrepancy score was related to the **Unstructured Task Total Points**,  $r=.366$ ,  $p<.01$  and the **Stroop Interference score**  $r=.383$ ,  $p<.01$ . The **Executive Dysfunction** discrepancy score was related to the **Stroop Interference Score**  $r=.303$ ,  $p<.05$  (See Figures 1A, 2A, and 3A). There were no other relationships with Apathy or Executive Dysfunction discrepancy scores. **Memory discrepancy** scores were unrelated to any predictor variable.

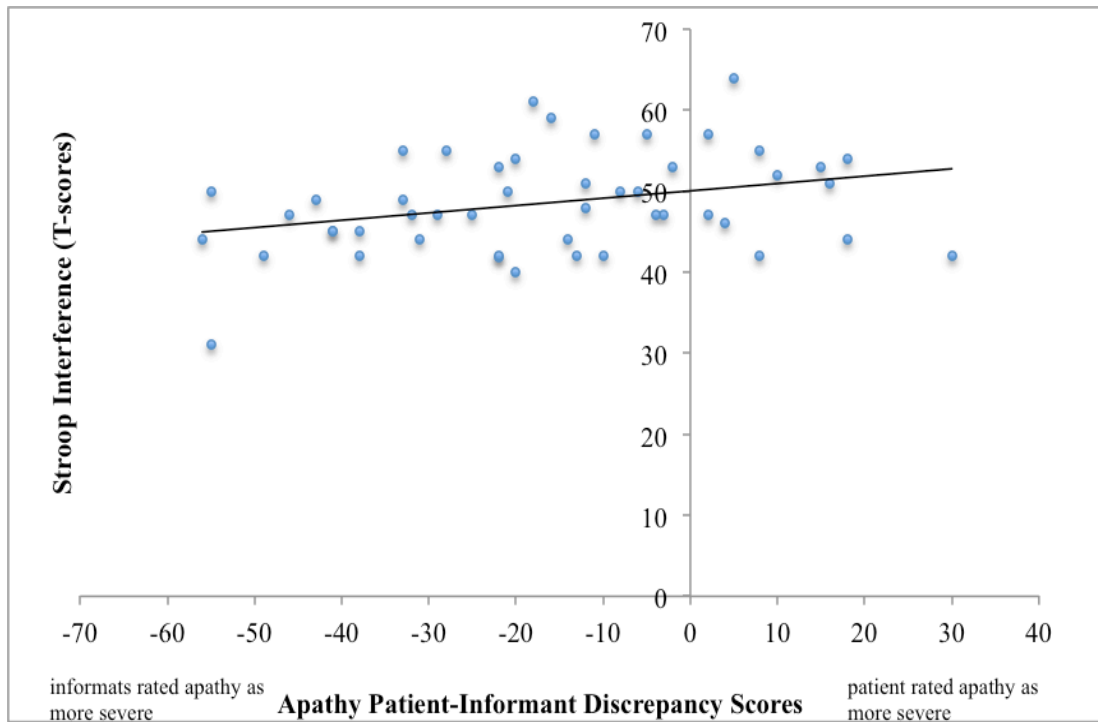
**Table 7A.** Correlations between main predictors and outcome variables for Metacognitive Knowledge.

	Unstructured Task Points	Stroop Interference	AES-C	HVLT-R
Memory Discrepancy	ns	ns	ns	ns
Apathy Discrepancy	.366**	.383**	ns	ns
EF Discrepancy	ns	.303*	ns	ns

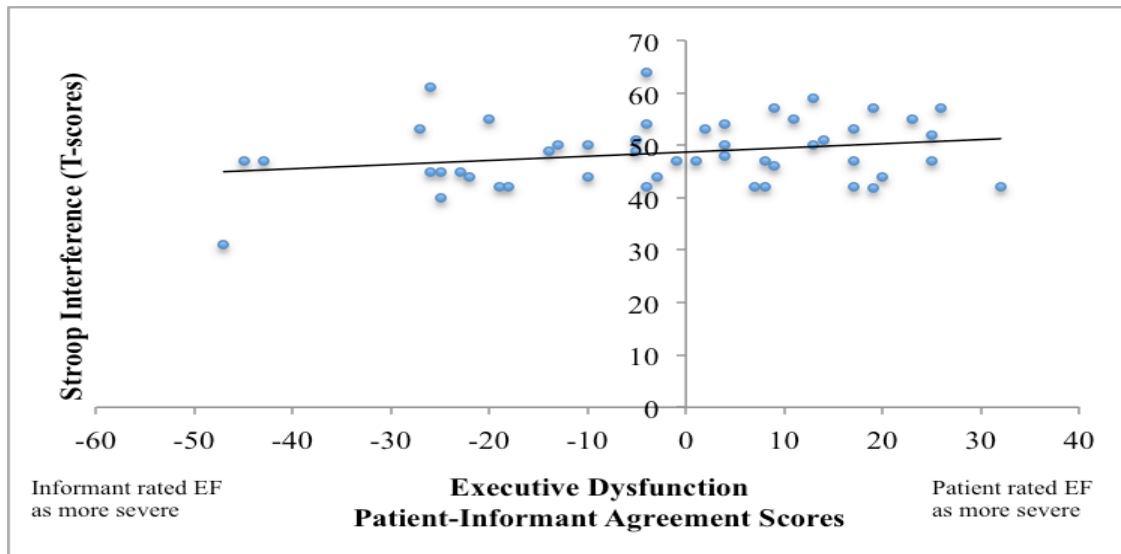
ns=not significant, \*\* p<.01, \* p<.05



**Figure 1A.** Relationship between Metacognitive Knowledge of Apathy and Unstructured Task Performance.



**Figure 2A.** Relationship between Metacognitive Knowledge of Apathy and Stroop Interference Scores.



**Figure 3A.** Relationship Metacognitive Knowledge of Executive Functioning and Stroop Interference.

### Correlations of Other HVLTR Memory Indices with Outcome Variables (MCK)

Exploratory analyses were also conducted to determine if different aspects of memory were associated with Metacognitive Knowledge. Analysis of all components of the HVLTR was used to explore which aspects of memory may be associated with anosognosia in HD. The HVLTR has been used in prodromal HD patients to measure learning and encoding using Trial 1 and Total Score, Retrieval using Delayed Recall Score and Storage using the Discriminability and Retention score (Solomon et al., 2007). **Apathy** discrepancy was related to the HVLTR Trial 1,  $r=.392$ ,  $p<.01$  and HVLTR Immediate Memory Total Standard Score,  $r=.342$ ,  $p<.05$ . There was a trending relationship between **Apathy** discrepancy and HVLTR Delay Raw Score,  $r=.24$ ,  $p=.097$ . There were no relationships between other HVLTR sub-scores and Executive Dysfunction or memory discrepancy scores.

**Table 8A.** Relationships between Metacognitive Knowledge and Memory.

	Trial 1	Total Score	Delayed Recall	Discriminability
Apathy Discrepancy	.392**	.342*	.24 <sup>+</sup>	ns
Executive Functioning Discrepancy	ns	ns	ns	ns
Memory Discrepancy	ns	ns	ns	ns

ns=not significant, + trending, \*\*  $p<.01$ , \* $p<.05$

### Correlations of Other Executive Measures with Outcome Variables (MCK)

To examine if different aspects of executive function are associated with Metacognitive Knowledge, correlations between the MCK outcome variables and each executive task was examined. Apathy discrepancy scores were related to the Stroop CW, Stroop Interference, and the Unstructured Task Total Points. Executive Dysfunction discrepancy scores were related to the Stroop Interference score (See Table 18).

**Table 9A.** Correlations between Executive Measures and Metacognitive Knowledge.

	TMT-B	TMT-B-A	Stroop CW	Stroop Interference	Unstructured Task Total Points
Memory Discrepancy	ns	ns	ns	ns	ns
Apathy Discrepancy	ns	ns	.295*	.383**	.366**
EF Discrepancy	ns	ns	ns	.303*	ns

ns= not significant; \* p<.05; \*\* p<.01

### Correlations of Other Factors and Outcome Variables (MCK)

In addition to hypothesized variables, there are several other non-cognitive or emotion related variables that were considered that either may be related to awareness or could explain results (See Table 19).

Regarding gender's relationship with Apathy discrepancy scores, the mean male discrepancy score (M=-25, SD=17.55) was higher than the mean female discrepancy score (M=-11, SD=21.93). While not a control variable, the Apathy discrepancy scores were also related to the standardized MoCA score,  $r=.399$ ,  $p<.01$ .

**Table 10A.** Relationships among Metacognitive Knowledge variables and control variables.

	Apathy Discrepancy	Executive Discrepancy	Memory Discrepancy
Age	ns	-.381**	-.294*
Gender	-.315*	ns	ns
Motor Scores	-.34*	-.287*	ns
Education	ns	ns	ns
Caregiver Burden	-.276, p=.055	ns	ns

ns= not significant; \* p<.05; \*\* p<.01

**Table 11A.** Metacognitive Knowledge Model without Motor Scores.

OLS Model	R <sup>2</sup> Model 1: Without Motor Scores	R <sup>2</sup> Model 2: With Motor Scores	R <sup>2</sup> Δ	F Value for R <sup>2</sup> Δ	Overall Significance for OLS Model
Apathy Discrepancy	.409	.411	.002	F(1,38)=.11, p=.742	No Motor: F(8,39)=3.376, p<.01 Motor: F(9,38)=2.945, p<.01
EF Discrepancy	.328	.326	.002	F(1,38)=.125, p=.726	No Motor: F(8,39)=2.358, p<.05 Motor: F(9,38)=2.063, p<.058
Memory Discrepancy	.285	.286	.01	F(1,38)=.003, p=.954	No Motor: F(8, 39)=1.948, p=.08 Motor: F(9,38)=1.541, p=.126

Model Fit:  $\chi^2(24)=52.317, p<.001$ .

The model without motor scores also did not deviate from multivariate normality,  $B_{1p}=0.79, X^2(10)=7.11, p=0.71, B_{2p}=13.48, z_{upper}=-0.97, z_{lower}=-1.73$  (See Table 21 and Figure 28 for results).

### **Apathy Awareness**

In the model excluding motor scores, Apathy Discrepancy scores were related to the Stroop Interference score (positive relationship) and the Unstructured Task total score (positive relationship). There was a trending relationship with the AES-C total score (positive relationship). The Wald test suggests that the coefficients for the AES-C and Stroop interference scores are not significantly different  $\chi^2(1)=1.038, p=0.31$ . The AES-C and Unstructured coefficients were also not significantly different  $\chi^2(1)=0.496, p=0.48$ . The Unstructured Task and Stroop coefficients were not significantly different  $\chi^2(1)=0.159, p=0.68$ .

### **Executive Functioning**

With motor scores excluded, the Executive Dysfunction Discrepancy scores were related to the HVLTR recognition score (negative relationship) and the Unstructured Task Norms (positive relationship). The coefficients were significantly different  $\chi^2(1)=8.682, p<.05$ .

### **Memory**

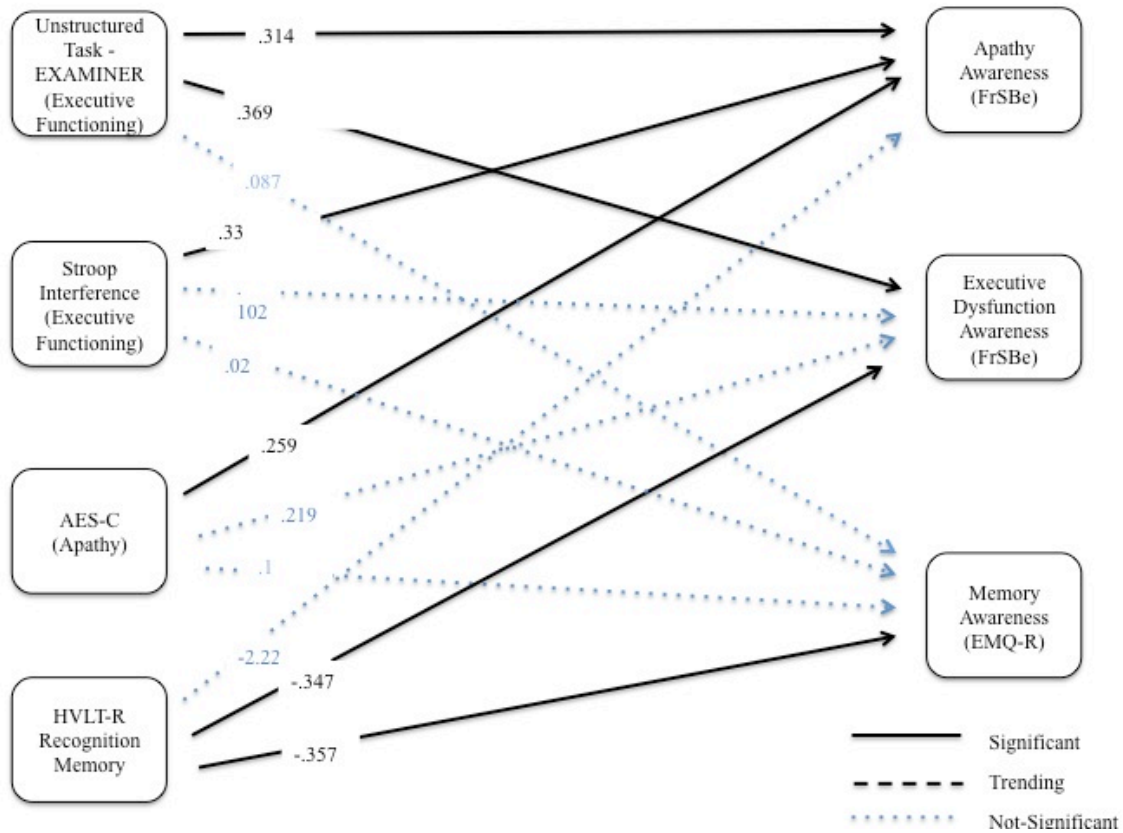
The Memory Discrepancy score was negatively related to the HVLTR recognition score.

**Table 12A.** Metacognitive Analysis without Motor Scores (48 participants).

	Apathy Awareness			Executive Awareness			Memory Awareness		
	Est.	SE	St. Est.	Est.	SE	St. Est.	Est.	SE	St. Est.
<b>Uns. Task</b>	<b>0.399*</b>	<b>0.170</b>	<b>0.314*</b>	<b>0.478*</b>	<b>0.185</b>	<b>0.369*</b>	0.117	0.198	0.087
<b>Stroop Int.</b>	<b>0.508*</b>	<b>0.208</b>	<b>0.330*</b>	0.161	0.227	0.102	0.032	0.242	0.020
<b>AES-C</b>	0.254+	0.130	0.259+	0.219	0.142	0.219	0.104	0.152	0.100
<b>HVLT-R</b>	-0.202	0.130	-0.215	<b>-0.329*</b>	<b>0.142</b>	<b>-0.343*</b>	<b>-0.361*</b>	<b>0.152</b>	<b>-0.362*</b>
Age	-0.003	0.012	-0.036	<b>-0.025*</b>	<b>0.013</b>	<b>-0.284*</b>	-0.025+	0.013	0.167+
Gender	<b>-0.531*</b>	<b>0.254</b>	<b>-0.271*</b>	0.087	0.276	0.044	0.015	0.296	0.007
Education	0.056	0.054	0.129	0.001	0.058	0.001	0.077	0.063	0.167
Care Burden	-0.253+	0.136	-0.263+	-0.291*	0.148	-0.296*	-0.407*	0.159	-0.398*

Main Predictors are bolded; \* p<.05; + p<.1; Uns. Task = Unstructured Task Total Points Standard Score; Stroop Int.=Stroop Interference Scores; HVLT-R=HVLT-R Recognition Scores; Care Burden= Caregiver Burden





**Figure 4A.** Multivariate Multiple Regression Results (no motor scores included).

Black indicates a significant path, Blue indicates a non-significant path. Standardized coefficients are reported in the figures.

## **APPENDIX F:**

### **ADDITIONAL ANALYSES FOR ANTICIPATORY AWARENESS**

#### **Correlations between Predictors and Anticipatory Awareness Variables**

With the removal of the influential data points from the final regression model (51 participants), only the AES-C was trending with immediate medication memory  $r=.284$ ,  $p<.05$ .

#### **Correlations between Additional Variables and Anticipatory Awareness Dependent Variables**

With the removal of influential data points, age was associated with address recognition memory,  $r=.479$ ,  $p<.001$ .

#### **Creating Prediction Discrepancy Factor Scores**

The intended analysis was to use a principal components analysis approach to create the overall Memory Prediction and Executive Function Prediction factor scores from each NAB task's prediction – performance discrepancy score. The purpose was to reduce the number of variables in the main regression analysis. Assumptions were met for the creation of a PCA factor score for executive function prediction; the judgment and driving prediction discrepancy scores were significantly associated  $r=.559$ ,  $p<.001$ . The KMO suggested adequate sampling (.5) and Bartlett's test of sphericity was significant  $\chi^2(1)=7.039$ ,  $p<.01$ . However, the relationships among some memory discrepancy scores were not significant, therefore one factor score could

not be created for “memory prediction.” It may also be more beneficial theoretically to examine these components of memory separately as they are typically associated with different processes (e.g. immediate memory – encoding, delay memory-retrieval, and recognition memory), therefore the creation of factors for these variables was explored. There were significant relationships between immediate memory for medication and address ( $r=.495$ ,  $p<.001$ ), between the delay memory for medication and address ( $r=.535$ ,  $p<.001$ ), and between recognition memory for medication and address ( $r=.384$ ,  $p<.01$ ). There was also adequate sampling ( $KMO=.5$ ) and Bartlett’s test of sphericity indicated PCA was appropriate for these variable pairs  $\chi^2(1)=14.78$ ,  $p<.001$  (immediate memory),  $\chi^2(1)=17.38$ ,  $p<.001$  (delayed memory), and  $\chi^2(1)=8.31$ ,  $p<.01$  (recognition memory). The created factors scores histograms were examined for normality. All factor scores had a normal distribution.

There was only a trending relationship between the executive factor predictor score and HVLT-R recognition raw scores,  $r=.232$ ,  $p=.091$ . The factor prediction scores were unrelated to any other predictor variable. Relationships were also examined between the factor scores and the control variables (age, gender, education, and motor scores). Age was associated with memory recognition prediction,  $r=.338$ ,  $p<.05$ . There was a trending relationship between motor scores and delayed memory,  $r=-.243$ ,  $p=.077$ .

**Table 13A.** Correlations between main predictors and outcome variables for Anticipatory Awareness.

<b>Anticipatory Awareness:</b>	AES-C	Stroop Interference	Unstructured Task	HVLT-R Recognition
Executive Factor	ns	ns	ns	.232, p=.091
Immediate Memory Factor	ns	ns	ns	ns
Delayed Memory Factor	ns	ns	ns	ns
Recognition Memory Factor	ns	ns	ns	ns

## **APPENDIX G:**

### **ADDITIONAL ANALYSES FOR EMERGENT AWARENESS**

#### **Correlations between Predictors and Emergent Awareness Variables**

Performance Evaluation scores were calculated by subtracting the patient ratings from the actual performance percentile for each NAB task and/or subtask. AES-C was related to medication immediate memory,  $r=.294$ ,  $p<.05$ . Age was associated with medication delay memory evaluation,  $r=.302$ ,  $p<.05$  and address delay memory evaluation,  $r=.348$ ,  $p<.05$ . No other relationships were detected.

#### **Creating Evaluation Discrepancy Factor Scores**

Assumptions were met for the creation of a PCA factor score for executive function evaluation; the judgment evaluation and driving evaluation scores were significantly associated  $r=.622$ ,  $p<.001$ . The KMO suggested adequate sampling (.5) and Bartlett's test of sphericity indicated was significant  $X^2(1)=25.194$ ,  $p<.001$ . Factor scores were also created for immediate memory evaluation (medication and address relationship,  $r=.701$ ,  $p<.001$ ), delay memory evaluation (relationship  $r=.609$ ,  $p<.001$ ), recognition memory (relationship  $r=.417$ ,  $p<.01$ ).

There was also adequate sampling (KMO=.5) and Bartlett's test of sphericity indicated PCA was appropriate for these variable pairs  $X^2(1)=35.54$ ,  $p<.001$  (immediate memory),  $X^2(1)=23.9$ ,  $p<.001$  (delayed memory), and  $X^2(1)=10.02$ ,  $p<.01$  (recognition memory). The

created factors scores histograms were examined for normality. All factor scores had a normal distribution. The only relationship present between factor scores and main predictors was the AES-C and the Recognition Memory score ( $r=.285$ ,  $p<.05$ ).

**Table 14A.** Correlations between main predictors and outcome variables for Emergent Awareness.

<b>Emergent Awareness:</b>	AES-C	Stroop Interference	Unstructured Task	HVLT-R Recognition
Executive Factor	ns	ns	ns	ns
Immediate Memory Factor	ns	ns	ns	ns
Delayed Memory Factor	ns	ns	ns	ns
Recognition Memory Factor	.285, $p<.05$	ns	ns	ns

**APPENDIX H:**

**Institutional Review Board Approvals**



RESEARCH INTEGRITY AND COMPLIANCE  
Institutional Review Boards, FWA No. 00001669  
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4799  
(813) 974-5638 • FAX (813) 974-7091

October 26, 2015

Danielle Hergert, M.A. Psychology

4202 E. Fowler Avenue PCD 4118G

Tampa, FL 33620

**RE: Expedited Approval for Initial Review**

IRB#: Pro00023422

Title: The Independent Contributions of Emotion and Cognitive Dysfunction on Anosognosia in Huntington's Disease Patients

**Study Approval Period: 10/25/2015 to 10/25/2016**

Dear Ms. Hergert:

On 10/25/2015, the Institutional Review Board (IRB) reviewed and **APPROVED** the above application and all documents contained within, including those outlined below.

**Approved Item(s): Protocol Document(s):** [Pro00023422\\_Protocol V1](#)

**Consent/Assent Document(s)\*:**

[Informant Consent\\_V1.pdf](#) [Patient Consent\\_V1.pdf](#) [Informant Online V1](#) \*\*granted a waiver

\*Please use only the official IRB stamped informed consent/assent document(s) found under the "Attachments" tab. Please note, these consent/assent document(s) are only valid during the approval period indicated at the top of the form(s). \*\*Waivers are not stamped.

It was the determination of the IRB that your study qualified for expedited review which includes activities that (1) present no more than minimal risk to human subjects, and (2) involve

only procedures listed in one or more of the categories outlined below. The IRB may review research through the expedited review procedure authorized by 45CFR46.110 and 21 CFR 56.110. The research proposed in this study is categorized under the following expedited review category:

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Your study qualifies for a waiver of the requirements for the informed consent process as outlined in the federal regulations at 45CFR46.116 (d) which states that an IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Your study qualifies for a waiver of the requirements for the documentation of informed consent as outlined in the federal regulations at 45CFR46.117(c) which states that an IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either: (1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or (2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Your study qualifies for a waiver of the requirement for signed authorization as outlined in the HIPAA Privacy Rule regulations at 45CFR164.512(i) which states that an IRB may approve a waiver or alteration of the authorization requirement provided that the following criteria are met (1) the PHI use or disclosure involves no more than a minimal risk to the privacy of individuals; (2) the research could not practicably be conducted without the requested waiver or alteration; and (3) the research could not practicably be conducted without access to and use of the PHI.

[A partial waiver of HIPAA Authorization is granted for recruitment purposes only; Authorization will be obtained as part of the informed consent process. Pursuant to this partial waiver, the study team is allowed to access the USF Huntington's Disease Research Registry to obtain PHI of patients who provided their informed consent to participate in the registry to determine whether they meet inclusion criteria for this study. ]

As the principal investigator of this study, it is your responsibility to conduct this study in accordance



with IRB policies and procedures and as approved by the IRB. Any changes to the approved research must be submitted to the IRB for review and approval via an amendment. Additionally, all unanticipated problems must be reported to the USF IRB within five (5) calendar days.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,



Kristen Salomon, Ph.D., Vice Chairperson

USF Institutional Review Board



UNIVERSITY OF  
SOUTH FLORIDA

9/28/2016

RESEARCH INTEGRITY AND COMPLIANCE  
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Danielle Hergert, M.A.

Psychology

4202 E. Fowler Avenue Tampa, FL 33620

**RE: Expedited Approval for Continuing Review**

IRB#: CR1\_Pro00023422

Title: The Independent Contributions of Emotion and Cognitive Dysfunction on Anosognosia in Huntington's Disease Patients

**Study Approval Period: 10/25/2016 to 10/25/2017**

Dear Danielle Hergert:

On 9/28/2016, the Institutional Review Board (IRB) reviewed and **APPROVED** the above application and all documents contained within including those outlined below.

**Approved Item(s): Protocol Document(s):**

[Pro00023422\\_Protocol V2\\_Jan182016\\_Clean](#)

The waiver of informed consent process, waiver of documentation of consent and the waiver of HIPAA

for recruitment/screening purposes only authorization have been renewed.

The IRB determined that your study qualified for expedited review based on federal expedited category number(s):

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

As the principal investigator of this study, it is your responsibility to conduct this study in accordance with USF HRPP policies and procedures and as approved by the USF IRB. Any changes to the approved research must be submitted to the IRB for review and approval by an amendment. Additionally, all unanticipated problems must be reported to the USF IRB within five (5) calendar days.

We appreciate your dedication to the ethical conduct of human subject research at the University of South Florida and your continued commitment to human research protections. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,



John Schinka, Ph.D., Chairperson

USF Institutional Review Board