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# Emotional Memory for Affective Words in Manifest and Prodromal Huntington's Disease

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Emotional Memory for Affective Words in  
Manifest and Prodromal 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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## ABSTRACT

Huntington's disease (HD) patients have been found to have specific deficits in emotional processing, most consistently demonstrating impairment recognizing the emotion expressed on a static face. The purpose of this study was to examine emotional memory in HD, which has not yet been investigated, and its relationship with executive functioning, emotional facial recognition, and the disease progression in HD. An emotional memory task with pleasant, neutral, and unpleasant words was administered to control (n=26), prodromal HD (n=26), and manifest HD (n=29) participants in addition to executive function measures, an apathy scale, and emotional facial recognition task. Free recall was not significantly different between groups. Using recognition sensitivity ( $d'$ ), prodromal HD participants did not demonstrate emotional memory enhancement, while manifest HD patients evidenced significantly lower emotional recognition relative to controls. Groups were significantly different on neutral word recognition. Emotional recognition sensitivity was related to disease progression, emotional facial recognition, and executive functioning, but not apathy. Regression models suggested that recognition for pleasant and unpleasant words have both shared and unique predictors, with executive dysfunction predicting affective recognition within both valences. Disease progression uniquely predicted unpleasant recognition while age was a negative predictor of pleasant recognition. These results suggest that impaired emotional memory is present in HD, progresses with the disease, and may evidence increased difficulty with negative emotional memory.

## INTRODUCTION

Emotional material, when compared to neutral material, benefits from increased cognitive processing, leading to increased memory for affective material (De Kloet, Joëls, & Holsboer, 2005; Kensinger & Corkin, 2003). Both limbic regions (specifically the amygdala) and prefrontal regions have been demonstrated to contribute to emotional memory enhancement (Kensinger & Schacter, 2006). While emotional memory enhancement is often maintained in a disease such as Alzheimer's disease, patients with frontal dysfunction (i.e., frontotemporal dementia) or patients with altered frontal dopaminergic networks (i.e., Parkinson's disease), no longer benefit from emotional memory enhancement (Hälbig, et al, 2008; Kumfor et al., 2013).

Emotional memory has not previously been examined in Huntington's disease (HD) despite significant emotional disturbance (psychopathology), impaired emotional facial recognition in these patients, and damage to prefrontal cortex and frontal-striatal dopamine pathways, which prior research suggests impacts emotional memory enhancement. This study will seek to examine emotional memory in HD, understand how it relates to emotional facial recognition, and examine factors that contribute to emotional memory impairment in HD, such as co-existing apathy and executive dysfunction. This paper will first review emotional memory enhancement and mechanisms through which enhancement is typically affected (e.g., attention, emotion regulation) and the current theories that seek to explain emotional memory. The proposed role of several structures will then be described, particularly the amygdala and regions of the prefrontal cortex. Results from studies exploring emotional memory and emotional processing in



neurodegenerative diseases will then be discussed, emphasizing their contribution to our understanding of emotional processing. The present study will add to the literature by examining emotional memory in Huntington's disease, which has not yet been described. An understanding of emotional memory through the framework of HD, given its unique neuropathology and clinical features, will add to the conceptualization of emotional memory. Further, this research may have clinical relevance by providing information on how to approach improving memory function in these patients as well as some insight into the mechanisms behind the emotional impairment experienced by patients and caregivers daily.

### **Emotional Memory Enhancement**

Enhanced memory has been defined by Richter-Levin (2004) to be “more persistent (i.e., long-lasting), stronger (i.e., resistant to disruptions), or more accurate, or a combination of the above (pg. 31).” Increased memory for emotional stimuli relative to neutral stimuli has been reported when examining memory for both affective words (Kensinger & Corkin, 2003) and affective pictures (Humphreys, Underwood, & Chapman, 2010; Palomba, Angrilli, & Mini, 1997). Emotional memories last much longer than neutral memories, with increased recognition of pictures found after delays ranging from 4 weeks (Hamann, Ely, Grafton, & Kilts, 1999) to one year after encoding (Dolcos, LaBar, & Cabeza, 2005). To account for this memory enhancement, several processes that have been proposed to contribute to emotional memory enhancement are described below, including enhanced perceptual processing (Pessoa & Adolphs, 2010), increased attention (Vuilleumier, Armony, Driver, & Dolan, 2001; Vuilleumier & Huang, 2009), level of processing at the time of encoding (Ritchey, LaBar, & Cabeza, 2011), and emotional regulation in response to a stimuli (Hayes et al., 2010).

## **Processes Contributing to Emotional Memory Enhancement**

**Enhanced perceptual processing:** Several imaging studies have demonstrated that emotional material (e.g., affective faces and voices) recruits primary sensory areas to a greater extent than neutral stimuli, as indexed by differences in levels of neural activation (Schupp, Junghofer, Weike & Hamm, 2003). Moreover, findings also demonstrate that increased level of activation is associated with actual increased perception of stimuli (Vuilleumier & Huang, 2009). For visual information, the amygdala is hypothesized to interact with primary sensory areas to increase processing of emotional material through both direct (amygdala – visual cortex) and indirect (amygdala – PFC – visual cortex) pathways (Pessoa & Adolphs, 2010). This is further evidenced by an increase in perceptual information that is stored with the memory. When shown affective words in colored ink, participants were better able to recall the color of ink that affective words were printed in relative to neutral words, demonstrating increased perceptual details in memory (Kensinger & Corkin, 2003).

**Increased attention:** When emotional material is shown to participants, it captures attention. Notably, this increased attention is not due to overt attention (number of fixations and total viewing time) which was found to increase memory for neutral pictures, but instead more cognitively based focus and attention increases memory for emotional images (Humphreys et al., 2010). Increased activation in visual perceptual areas for emotional images (relative to neutral images) is considered to be evidence for early selective attention (Schupp, Junghofer, Weike, & Hamm, 2003). Similarly, when participants are shown affective words or pictures, they demonstrate an increased Late Parietal Positivity (LPP) occurring around 600-1000ms after stimulus exposure (Balconi, Falbo, & Conte, 2012; Citron, 2012). The LPP is an event related

potential (ERP) component that has been proposed to be a measure of increased attention allocation and increased attentional capture due to emotional content. Further, this increased attention correlated with better recall after a delay, an effect termed “the subsequent memory effect” (Friedman & Trott, 2000). Lastly, within a divided attention paradigm, attention has been reported to be maintained for emotional targets despite non-affective distractors while emotional distractors have been shown to capture attention from non-affective targets (Vuilleumier, Armony, Driver, & Dolan, 2001; Vuilleumier & Huang, 2009). For example, when told to selectively attend to one stimulus or the other (emotional faces vs. houses), normal participants demonstrated increased facial area activation on fMRI, even when attending to houses.

**Level of processing:** Level of processing during encoding has been found to sometimes surpass the influence of valence and arousal on neural activation in response to emotional stimuli (Dolcos, Denkova, & Dolcos, 2012). When encoding emotional material, shallow processing (e.g., focusing in perceptual features of a picture) causes greater amygdala activation, while deeper processing (e.g., focusing on the emotional content or meaning of a picture) results in more activation from the PFC, which likely reflects the more complex cognitive demands of the task (Ritchey, LaBar, & Cabeza, 2011). Taylor, Phan, Decker, and Liberzon (2003) examined PET scans while participants either rated the valence of emotional pictures vs. passively viewed them and found that the active viewing condition (ratings) decreased activation in limbic regions and increased activation in medial Prefrontal Cortex (mPFC). Other researchers have proposed that limiting cognitive processing (e.g., shallow encoding or divided attention) consistently increases emotional memory, noting that emotional words are often more “interesting” and are more likely to produce elaborative processing (Talmi, 2013)

**Emotion regulation:** Phillips et al. (2003) proposes that emotional regulation is a core step in processing of emotion stimuli and is often neglected. Both emotional memory and cognitive processes (as indexed by later ERP components, including the LPP) can be altered when participants are directed to use emotional regulation strategies, such as reappraisal and suppression. In the context of these studies, reappraisal is directed effort to reinterpret a situation or to change an emotional response while suppression is the purposeful inhibition of expressive behavior of an emotion, which typically does not alter the actual emotional response (Goldin, McRae, Ramel, & Gross, 2008). The use of reappraisal when exposed to emotional stimuli causes participants to evidence decreased ERP amplitude in response to emotional stimuli and enhanced emotional memory (Hajcak & Nieuwenhuis, 2006; Hayes et al., 2010). However, when suppressing emotional responses, emotional memory is decreased but ERP amplitudes remain intact (Gross & John, 2003; J. P. Hayes et al., 2010). Neuroimaging studies suggests that decreased emotional memory when using suppression techniques is associated with decreases in amygdala and hippocampal coupling, making the material less likely to be remembered (Hayes et al., 2010). Interestingly, Hayes et al. (2010) also found that those who rated pictures, which likely acts as a form of emotion regulation similar to reappraisal, rated their overall affect as better than those who passively viewed.

Emotional content naturally impacts automatic perceptual processing and attention. However, cognitive factors, such as the level of processing at encoding or emotional regulation strategies during encoding, can modify the degree to which an emotional memory enhancement is found. To understand how these processes interact, the current theories of emotional memory will be discussed, describing the automatic and controlled processes that are present in emotional memory.

## **Theories of Emotional Memory**

Several theories have been proposed to explain emotional memory. However, the current theories fail to offer a parsimonious account of emotional memory enhancement. The modulation hypothesis, described by McGaugh and Roozendaal (2002) and further by Roozendaal, McEwen, and Chattarji (2009), specifically focuses on the stress response and activity of the amygdala within these contexts. This theory proposes that both for short-term benefit and long term benefit, the amygdala releases stress hormones that modulate the consolidation of the memory, thus enhancing emotional memories. These stress hormones cause greater activation in medial temporal lobe (MTL) and amygdala, plus increased interaction between the two. The basolateral nucleus of the amygdala (BLA) is hypothesized to be the primary source for mediating the influence of epinephrine and glucocorticoids on the emotional memory process (McGaugh & Roozendaal, 2002). However, there are several shortcomings of this theory. The proposed mechanisms primarily rely on arousal (Hermans et al., 2014). Additionally, the modulation theory is grounded in the animal literature and fails to account for all phenomenon found in human emotional memory studies, despite several differences in processing between animal models and human processing (Badgaiyan, 2010). Critics of this theory have noted that although the amygdala and slower autonomic responses are activated in response to stimuli, these systems are not able to account for several aspects of emotional memory in humans (Hamann, 2001).

The mediation theory was proposed by Talmi (2013) to explain the disconnect between modulation theory and results of experimental findings in human studies. She noted that modulation theory did not account for immediate enhancement of emotional memory (e.g., within a 10-minute delay) and could not explain preferential processing for emotional over neutral items when stimuli are interspersed. She proposed that cognitive factors, such as the distinctiveness and

organization of the stimuli, interacted with consolidation factors to produce these immediate effects. However, the mediation theory still fails to account for positive valence, which does not always trigger a response that causes the release of hormones that modulate delayed memory. Additionally, the theory cannot account for the differences often observed between the animal and human literature, which is less reliant on fear-based paradigms and includes paradigms that often involve non-arousing valenced material.

**Valence and arousal.** Emotional stimuli vary on both valence (i.e., how positive or negative) and arousal (i.e., how exciting or calming) dimensions (Kensinger & Corkin, 2004). Though emotion is proposed to vary on these dimensions, researchers disagree on the relative importance of valence and arousal. Specifically, some researchers fail to separate the valence and arousal of a stimulus, using “emotional” interchangeably with arousing information (Levine & Pizarro, 2004) or disagree on the relative importance of key neuroanatomical areas. From an evolutionary perspective, researchers have proposed completely separate functions for positive and negative emotions. Levenson (1999) states that while negative emotions appear to be an “escape from homeostasis” to enact a plan of action, positive emotions serve to “undo” arousal and soothe, therefore returning to homeostasis. Relative to neutral words, those with negative valence were better remembered than neutral, but not as well as negative arousing words, suggesting enhancements due to both valence and arousal (Kensinger & Corkin, 2003).

In the Arousal Biased Competition (ABC) Theory, Mather and Sutherland (2011) describe their theory of how arousal enhances attention, perception, and memory for emotionally arousing items. Specifically, arousal enhances attention for goal relevant material and, therefore, increases memory for that material. They then describe how emotional information can impact both bottom-up processes (e.g., arousal will make contrast stand out more) and top-down processes (e.g.,

arousal will increase perception of goal relevant info). The ABC theory posits that, beyond arousal, priority is given to items that are: unexpected (due to the mismatch between what is expected and what is perceived), have emotional quality, or have social relevance. However, this theory is centered on the impact of arousal and fails to account for the relative importance of valence and enhanced memory and processing that occurs in the absence of high arousal.

Many authors acknowledge the involvement of two systems in play when emotional stimuli are encountered: A bottom-up system involving the amygdala and medial temporal lobes, and a top down system involving the prefrontal cortex. Though the relative importance of each system in emotional memory enhancement is debated, the amygdala and PFC have been consistently implicated through a variety of methods. Dolcos et al. (2012) suggests that while both routes are sensitive to arousal, valence has effects primarily through the PFC. Kensinger and Corkin (2004) proposed distinct processes for valence and arousal. They suggested that while arousal utilizes automatic processes (via the limbic system), valence operates through rehearsal, semantic elaboration, and “autobiographical identification,” or controlled processes orchestrated through the PFC. Dolcos et al. (2012) supports this view and further suggests that the PFC is sensitive to positive (or rewarding) self-relevant processes through reward circuitry.

### **Neuroanatomy of Emotional Memory**

As noted above, theories of emotional memory are often intertwined with proposals for the function of neuroanatomical structures, most consistently the amygdala and PFC and their connections. While many attempts have been made to create a one-to-one relationship between affect and brain regions, these models have consistently failed and evidenced overlapping activation (Hamann, 2012), or a shared network of activation (Lindquist et al., 2015; see Man,

Nohlen, Melo, & Cunningham, 2017 for review). However, consistent activation of several areas across studies indicates that some areas may respond to certain processes, providing insight into the mechanisms underlying emotional memory enhancement.

**The amygdala.** The amygdala receives projections from higher stages of sensory processing (Rolls, 2015), but also interacts with primary sensory areas to increase processing of emotional material through both direct (amygdala – visual cortex) and indirect (amygdala – PFC – visual cortex) pathways (Pessoa & Adolphs, 2010). Increased amygdala activation has been consistently reported in response to stimuli of significance (e.g., emotional faces), even with limited attention (Vuilleumier & Huang, 2009). Further, habituation of amygdala response to emotional stimuli with repeated exposure has also been reported (Phillips et al., 2003), suggesting that novelty has some relationship to the initial activation. The amygdala is activated when participants are presented with both positive and negative valenced stimuli regardless of arousal (Hamann et al., 1999), though some contend that its activation is more consistently associated with the presence of high arousing stimuli regardless of valence (Hermans et al., 2014; Kensinger & Corkin, 2004; Lewis et al., 2007; Sharot et al., 2007).

In emotional memory, the amygdala is hypothesized to be involved in encoding, consolidation, and retrieval of emotional stimuli (Dolcos et al., 2012), with interaction between the amygdala and hippocampus predictive of increased memory (McGaugh, 2004). Indeed, the level of amygdala activation is proposed to be a mechanism for enhancement of memory observed over a delay period, with activation of the amygdala positively correlated with increased subsequent memory (Hamann et al., 1999). Some researchers even suggest that the amygdala activation is the primary mechanism of plasticity in emotional memory and learning (LeDoux, 2007).



Notably, increased amygdala activation is also associated with other types of cognitive processes, often making it difficult to tease apart the cause of activation. Regardless of affective content, amygdala activation has been reported in processing of items that are salient, are significant or relevant to the individual or current cognitive processing demands, and when unpredictability is present (Kensinger & Corkin, 2004; Pessoa & Adolphs, 2010; Vuilleumier & Huang, 2009). Activation is also reported for visual stimuli alone, particularly ambiguous images (Vuilleumier & Huang, 2009) that involve external cue interpretation (Damasio et al., 2000; Phan, Wager, Taylor, & Liberzon, 2002) and in goal directed tasks (Banich et al., 2009).

Prior research suggests that amygdala removal results in the loss of gist (as opposed to detail) information in memory, suggesting it does not just directly modulate sensory processes, but also interacts with frontal regions to extract conceptual information (Hermans et al., 2014). Studies find that when the amygdala is surgically removed, that these patients develop immediate emotional memory enhancement, but lack long term enhancement of this same material (Hermans et al., 2014). Patients with amygdala damage also remember more emotional words low in arousal relative to neutral words, suggesting PFC and MTL involvement with valence in the absence of arousal (LaBar & Cabeza, 2006). LaBar and Cabeza (2006) further suggest that amygdala activation aids in emotion and cognition interaction, which is consistent with the proposal of Pessoa (2008), who describes the amygdala as a “hub” for emotion and cognition interactions.

In summary, amygdala activation alone cannot account for emotional memory enhancement. Taken together, the amygdala is consistently activated when examining emotional memory processing. However, the role of the amygdala is not entirely understood and there has yet to be a unifying theory of emotional memory explaining its involvement in enhanced immediate emotional memory and separating the activation to emotional stimuli from other

cognitive processes. Despite the strong focus on the involvement of amygdala activation, activation of areas of the prefrontal cortex is also found to play a large role in perceiving, interpreting, and evaluating emotional stimuli and in emotional memory.

**The prefrontal cortex (PFC).** The PFC has been divided into subregions with an emphasis on connectivity to other brain regions and function (Siddiqui, Chatterjee, Kumar, Siddiqui, & Goyal, 2008). The most important regions of the PFC often recruited for emotional processing are the anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC), with the subregions of the mPFC often being difficult to differentiate (Etkin, Egner, & Kalisch, 2011; Kringelbach, & Rolls, 2004). However, some distinguish key regions of the mPFC, including the ventromedial prefrontal (vmPFC) and the orbitofrontal cortex (OFC), though the OFC is difficult to separate from the vmPFC due to overlapping areas in the medial regions (Kringelbach, & Rolls, 2004).

**Anterior cingulate cortex (ACC).** Some research suggests that activation of the ACC may be associated with the ability to disengage and attend to more emotionally arousing (priority) stimuli (Mather & Sutherland, 2011). Additionally, recruitment of the ACC is proposed when storing emotional/reward value in memory (Rolls, 2015) and in determining the costs and benefits of action, even when the material is not emotional (Pessoa, 2008). The ACC is further proposed to have both cognitive (dorsal) and emotional (rostral) divisions that differentially activate depending on the cognitive processes (Bush, Luu, & Posner, 2000). Activation of the ACC has also been reported for socially relevant stimuli and imagining positive events (Sharot et al., 2007). Lastly, Catani, Dell'Acque, and De Schotten (2013) proposed the default network, which involves the anterior cingulate-medial PFC and posterior cingulate-precuneus, is de-activated during goal-directed tasks (e.g., working memory, introspection, self-directed thought). The default network is further suggested to be activated between encoding and retrieval in memory tasks, possibly aiding

in the enhanced memory seen after a delay through the formation of associations in memory (Bar, 2007; Hermans et al., 2014). Buckner, Andres-Hanna, and Schacter (2008) further suggest that the default network may aid in mental representations of imagined emotional events and inferred emotion. In lesion studies, patients with bilateral cingulotomy were suggested to have decreased emotional experience, self-initiated behavior, and intention (Cohen et al., 2001).

A meta-analysis revealed the insula and ACC are activated during cognitively demanding encoding tasks (compared to passive viewing) and in mood induction paradigms when asked to recall or imagine an emotional scene or event (Phan et al., 2002). Hermans et al. (2014) suggest that the insula is part of the “salience network” and may act to mark events for further processing, though some suggest the insula simply responds to autonomic activation (Rolls, 2015). When presented with primary sensory stimuli, insula activation is observed in association with intensity but not valence (Rolls, 2015). It has also been associated with activation in response to “conflicting” items (Citron, 2012). Lastly, Rolls (2015) noted the insula is activated when decoding reward/punishment information that can produce autonomic/visceral responses. The insula is often activated by emotional stimuli (especially expressions of disgust) and may be used to interpret what is happening to body/interceptive sensations/feelings. The subgenual cingulate cortex is noted by Maddock, Garrett, and Buonocore (2003) to be most consistently activated when rating the valence of emotional words. They further suggest that it is related to valence, regardless of stimulus type (i.e., both pictures and words).

**Medial prefrontal frontal cortex (mPFC).** Mather and Sutherland (2011) suggest that medial prefrontal cortex interacts with parietal areas to influence perception of arousing (i.e., priority) information. The mPFC has a general role in emotional processing, which is found across emotional categories and stimuli type (Phan et al., 2002). While some studies discuss the mPFC

as a whole, other researchers have suggested distinct functional networks within the mPFC (Hornak et al., 2003), consisting of the OFC, which demonstrates increased activation in response to valence (Northoff et al., 2000, Lewis, Critchley, Rotshtein, & Dolan, 2007), and the vmPFC, which activates when integrating cognitive and emotional information (Roy, Shohamy, & Wager, 2012).

*Ventromedial prefrontal cortex (vmPFC):* Though implicated in a wide array of cognitive processes, the vmPFC is suggested to activate when integrating cognitive-emotional information more globally, with one function being evaluative and the other connecting affect and memory (Roy, Shohamy, & Wager, 2012). The vmPFC is proposed to use evaluative information from the OFC in decision-making (Rolls, 2015). Additionally, activation on PET scanning was related to subjective negative affect (Zald, Mattson, & Pardo, 2002). Lastly, patients with vmPFC damage have specific difficulties identifying emotional faces, with impairment extending across all emotions (Heberlein, Padon, Gillihan, Farah, & Fellows, 2008).

*Orbitofrontal cortex (OFC):* The temporal-amygdala-orbitofrontal network, of which the OFC is part, is implicated in behavioral inhibition, reward associations, outcome monitoring, multi-sensory integration, and memory for complex visual/temporal information (Citron, 2012). The OFC has been shown to be activated when assessing reward value in humans, providing evaluative information to the dorsolateral PFC (dlPFC) for decision making (Rolls, 2015). The OFC is proposed to be activated in relation to both positive and negative valenced stimuli (Citron, 2012; Maddock, Garrett, & Buonocore, 2013, Kuchinke et al., 2005), and representations of reward (e.g., money) and expected reward (Rolls, 2015). A differentiation between medial and lateral portions of the OFC has been proposed, with medial regions activated in response to negative pictures and words, and lateral regions demonstrating weaker, though distinct, activation

to positive words and pictures (Northoff et al., 2000, Lewis, Critchley, Rotshtein, and Dolan (2007). In OFC lesions, regardless of how small, patients have difficulty with 1) subjective emotional experience; 2) social behavioral difficulties (not responding appropriately to others emotional needs, such as comforting others), and 3) affect recognition, with impaired voice expression identification more consistently found than impairment on emotional facial recognition tasks (Hornak et al., 2003).

In summary, the prefrontal cortex, particularly the activation of ACC and mPFC regions, is involved in emotional processing and emotional memory. Some authors have suggested that while ACC activation aids increasing attention to emotional stimuli, the OFC activates in response to valence, with the vmPFC responding to integrating emotional and cognitive information for effective storage of emotional memories. These roles suggest the ACC and mPFC play important roles in emotional memory and emotional processing.

Given the importance of the amygdala and PFC regions, damage to these areas in the course of a neurological disease provides deficits in some of the key areas for emotional processing. Next, Alzheimer's disease (AD), Frontotemporal dementia (FTD), and Parkinson's disease (PD) will be examined to provide a conceptual foundation for investigation of emotional memory in Huntington's disease patients.

### **Neurodegenerative Diseases and Emotion Deficits**

Disease models provide unique insight into emotional processing, impacting specific system structures (e.g., hippocampus), large areas of the brain (e.g., prefrontal cortex) or neurotransmitter systems (e.g., dopaminergic system). While lesion studies have been beneficial, disease models with known anatomical progression can provide examination of changes over time

(or stages of disease) and aid in understanding the more complex systems of emotion processing. In one of the only models for emotional memory enhancement in neurodegenerative disease, Broster, Blonder, and Jiang (2012) elaborate on the observations of Borg et al. (2011) in Alzheimer's patients and suggest that emotional memory enhancement is determined by executive functioning. Broster, Blonder, and Jiang (2012) propose that those with severe impairment experience a decrement in emotional memory, while mild executive impairment produces either normal memory or slightly reduced emotional memory. This is also aligned with the conceptualization proposed by Pessoa (2009), in which he notes that emotion can impair or enhance memory depending on the interaction with executive abilities.

**Alzheimer's disease (AD).** AD is primarily defined by initial hippocampal atrophy (i.e., medial temporal lobe) with posterior cingulate and temporoparietal atrophy amid amyloid plaques and tau tangles (Sperling et al., 2011). Emotional memory is more widely researched in Alzheimer's disease than in other neurodegenerative diseases and allows for investigation of the importance of basic memory deficits in emotional memory enhancement.

Several studies have shown emotional memory enhancement is still present in AD. Kazui et al. (2000) presented twenty-five AD participants and ten healthy controls with a negatively arousing story and a neutral story, accompanied by photographs, and found both groups evidenced better recall for the emotional story. However, differences in arousal between the negative and neutral stories makes clear interpretation of these findings difficult. In another study using immediate recall of positive, negative, and neutral words (equated on arousal), Fleming, Kim, Doo, Maguire, and Potkin (2003) compared AD patients to controls (both younger and older). They found that AD patients recalled more emotional words across three trials relative to neutral words, with specific effects found for increased negative compared to neutral word recall. Using a deeper

encoding task (showing each word on a card, having the participant read it aloud, and discuss what the word meant to them and brought to mind), Kalenzaga, Piolino, and Clarys (2014) concluded that AD patients did not exhibit an emotional memory effect when “familiarity measures” were used (i.e., overall recognition accuracy using remember/know judgments). However, when specifically examining recollection (i.e., participant distinctly remembered the word and could provide similar details given at encoding) both groups demonstrated an enhancement for words “remembered” compared to familiar (i.e., “know” responses). Notably, arousal was not controlled for and controls also failed to demonstrate an emotional memory benefit, recognizing both neutral and emotional words at the same frequency.

Kensinger (2009), however, suggests that several studies have found that AD patients fail to show emotional enhancement. Notably, one such study used affective picture recognition after a 30-minute delay, without controlling for arousal, which evidenced near perfect performance in the control group and poor recognition in AD without emotional enhancement of memory (Abrisqueta-Gomez, Bueno, Oliveira, & Bertolucci, 2002). When using emotional and neutral stories in over 80 AD participants, Kensinger, Anderson, Growdon, and Corkin (2004) examined emotional memory (recall and recognition) after a ten-minute delay in AD and a 24hr delay in controls and again did not find emotional memory enhancement in AD patients. They suggested: 1) the amount of amygdala atrophy in AD may be enough to reduce the enhancement, 2) the modality in which the material was received (i.e., verbal story) did not create a strong enough “memory trace,” or 3) the stories were not arousing enough to benefit from emotional enhancement. Notably, previous research has found the magnitude of decreased amygdala volume in AD is associated with decreased memory for emotional content (Perrin et al., 2012). Additionally, Klein-Koerkamp et al (2012) suggests that emotional memory in AD can be

influenced by 1) task difficulty (too hard or easy for either group), 2) emotional memory task type (e.g., recollection responses, such as free recall, are more likely than know responses in recognition memory to evidence emotional enhancement effects), and 3) stimulus characteristics (e.g., arousing or self-referent material is more likely to be remembered). Lastly, the model proposed by Broster, Blonder, and Jiang (2012), based on findings from Borg et al. (2011) suggests that the most severely impaired AD cases (i.e., experiencing impairment in executive function) will be less likely to have emotional memory enhancement. It may be that disease severity and/or magnitude of amygdala atrophy across AD studies may account for discrepancy in findings.

Alzheimer's patients appear to have intact emotional facial recognition, even in moderate to severe AD (Guaita et al., 2009), however, they appear to overcompensate with more activation of "emotion circuits" to complete tasks rather than relying on more basic frontal cognitive processes like control participants (Rosenbaum, Furey, Horwitz, & Grady, 2010). Preserved emotional memory despite dementia in AD suggests that emotional memory may have specific networks that are not inherently impaired in the degenerative process of AD and which may depend on the degree of amygdala atrophy. The patterns found in AD inform other dementias, including Frontotemporal dementia, Parkinson's disease, and Huntington's disease, which are described next.

**Frontotemporal dementia (FTD).** While a lot of the emotional memory research has been devoted to examining the role of the amygdala in emotional memory, several frontal and subcortical regions are also important for emotional processing and emotional memory, as evident through disease models. For example, in FTD, which typically evidences less amygdala atrophy than AD but more temporal and frontal atrophy (Boccardi et al., 2002), FTD patients consistently fail to demonstrate any emotional memory enhancement (Kumfor, Irish, Hodges, & Piguet, 2013;



St. Jacques, Grady, Davidson, & Chow, 2014). For example, in a study examining all types of FTD (i.e., semantic, behavioral, and progressive non-fluent aphasia), AD, and controls, both the AD and control participants evidenced increased emotional memory for pictures, but those with any type of FTD did not (Kumfor et al., 2013). Importantly, this was a *relative* advantage of emotional material over neutral material; although the AD group remembered much less overall than the FTD group, emotional pictures were better remembered than neutral in AD, while in those with FTD, neutral and emotional memory were not significantly different. The neuropathology of FTD demonstrates atrophy of bilateral vmPFC, posterior OFC, and insula, and left ACC, all of which are described above as part of emotional processing networks (Rosen et al., 2002). Additionally, given that the amygdala is relatively spared in FTD (Rosen et al., 2002), it suggests that an intact amygdala alone is likely not sufficient to produce emotional memory enhancement. This is further supported through the fMRI neuroimaging findings, which suggest overall memory performance for neutral and negative pictures is correlated with activation in one set of structures (hippocampus, precuneus and posterior cingulate) while emotional memory enhancement (through a yes/no recognition paradigm) was associated predominantly with the orbitofrontal cortex (Kumfor et al., 2013). In a similar study, Kumfor, Irish, Hodges, and Piquet (2014) examined AD and the behavioral variant of FTD (bvFTD), comparing memory was for an emotional and neutral story. AD patients recalled more of the emotional story (emotional enhancement), while bvFTD did not demonstrate differences between the two stories. Further, they found that in AD, emotional memory enhancement was associated with increased activity in hippocampus, parahippocampus, and fusiform, while in bvFTD, increased activity in the orbitofrontal cortex, right amygdala and right insula were related to emotional memory enhancement. This is consistent with similar results found when examining another form of FTD, Progressive Non-fluent Aphasia (PNFA), compared

to AD (Kumfor, Hodges, & Piguet, 2014). In this study, AD participants again recognized an emotional story better than a neutral story (as did controls), but PNFA patients did not. The authors propose these findings suggest a widespread emotional processing deficit in PNFA.

Similarly to FTD, amyotrophic lateral sclerosis (ALS) patients have trouble with emotional facial recognition and emotional memory. ALS patients have difficulty discerning negative facial expressions, do not show emotional enhancement with emotional words, and are not able to accurately rate arousal and valence of words (Sedda, 2014). Pinkhardt et al. (2006) conclude that the frontal areas, more than temporal areas, appear to be the most impacted in ALS, despite some cell loss in the amygdala.

In conclusion, FTD patients are known to experience PFC degeneration with relatively intact amygdala and evidence consistent impairments in emotional memory. This impairment is also seen in ALS, which also evidences frontal impairments. This may suggest that frontal networks are an important part of emotional memory enhancement in neurodegenerative diseases, as suggested by Borg et al. (2011). Next we will explore Parkinson's and Huntington's disease, both of which are characterized by subcortical degeneration and disruption to dopaminergic pathways in frontal cortices.

**Parkinson's disease (PD).** Unlike AD, FTD, and ALS, PD is marked by specific cell death in the substantia nigra, causing specific, targeted disruptions in the nigrostrial dopaminergic pathway (Dauer & Przedborski, 2003). As such, PD patients experience disrupted dopaminergic frontal networks. In one of the few studies examining emotional memory in PD, Hälbig, et al. (2008) examined the ability of patients on and off dopaminergic medications to immediately freely recall affective pictures. They found that patients off medication (i.e., dopamine deficient) evidenced emotional memory enhancement while those on medication (i.e., increased dopamine)

did not. They concluded that higher level of dopamine might impair emotional memory as the dose of dopaminergic medication is established based on motor symptoms (nigrostriatal pathway), but may cause excessive dopamine in other pathways (specifically, mesocortical and mesolimbic pathways). Notably, this study used a general “emotional” category, which included arousing pictures from both positive and negative categories.

In a similar study using more stimuli and examining recognition memory, Hälbig et al (2011) attempted to distinguish the role of valence, controlling for arousal, in emotional memory in PD. They found that while off medication patients recognized more negative pictures after a 10-minute delay, positive pictures were remembered the most when on medication (like controls). Importantly, this was relative enhancement, with negative memory being significantly lower for negative pictures on medication and positive memory remaining relatively consistent. They concluded that dopamine’s impact on emotional memory is primarily through valence and not arousal, with dopamine adversely impacting the pattern of emotional memory. When comparing the results of Hälbig et al. (2008), this study demonstrates the importance of differentiating valence (positive and negative, rather than a general “emotional” category), considering arousal, and possibly suggests differences due to paradigms used (i.e., free recall vs. recognition). It is possible that the negative bias, paired with effects of arousal, contributed to the findings of Hälbig et al. (2008), indicating blunted emotional effects when on medication. As noted above, these factors (i.e., task difficulty, type, and stimuli characteristics) are also proposed to impact emotional memory in AD (Klein-Koerkamp et al., 2012). Contrary to these findings, a study using deep brain stimulation of the subthalamic nucleus in PD found stimulation uniquely increased immediate emotional memory compared to off medication (Schneider et al., 2003). No differences were found with delayed memory or in performance between on medication and stimulation conditions.

Notably, the stories were arousing in nature and participants reported higher arousal during the stimulation condition, which may suggest that enhancement occurred due to arousal. This may explain differences with Hälbig et al. (2011) and Hälbig et al. (2008), which suggest effects due to valence.

Bowers et al. (2006) examined PD startle reflex in response to emotional pictures (IAPS), which is suggested to be related to amygdala activation. PD patients demonstrated reduced startle reflex. They also rated negative pictures as less arousing (relative to controls), but did not differ in valence ratings. Further, these differences were related to disease progression (measured by Hoehn-Yahr stage). They suggest this could be related to “amygdala inhibition,” specifically referring to the continued inhibition of the amygdala from frontal cortex despite motivationally relevant stimuli that typically “release” the amygdala. In regards to emotional facial recognition, PD patients demonstrate inconsistent results, but generally have difficulty identifying affective expressions and prosody (Péron, Dondaine, Le Jeune, Grandjean, & Vérin, 2012), specifically regarding negative affect (Wieser et al., 2006). Lin, Tien, Huang, Tsai, and Hsu (2016) found that as PD progresses patients begin to not only experience impairment in negative emotions, but eventually positive emotion in the most progressed patients. They argue this impairment is not merely due to impaired facial processing, as patients could identify gender and happiness relatively easily. They further suggest that the circuits connecting the basal ganglia to frontal regions is specifically involved in the processing of emotions and that these results provide evidence this circuit is indicated in all emotions (i.e., including positive), as well as deteriorating communication between the PFC and amygdala. Further suggested explanations of these impairments suggest amygdala impairment (with increased BLA volume loss found in PD) or dopaminergic pathways, which project to prefrontal regions (Péron et al., 2012).

Overall, PD patients evidence reduced emotional memory enhancement when on dopaminergic medication (i.e., with higher levels of dopamine), possibly due to increased dopamine in cortical projections. Further, through studies with PD patients, the effects of dopamine have been proposed to be related to valence, rather than arousal, with the disease of PD related to increased emotional memory for negative stimuli (i.e., off medication, dopamine deficient), and an influx of dopamine (i.e., on medications) causing reduced negative emotional memory to align with controls and emotional enhancement of positive stimuli. Huntington's disease, which also evidences altered dopaminergic systems in frontal projections, will be explored in the next section of this paper.

### **Huntington's Disease and Emotion**

HD is an autosomal dominant genetic disorder characterized by cell loss in the basal ganglia (BG), specifically the caudate nucleus. Inheritance is determined by expansion of the Huntingtin gene on chromosome 4 by extra CAG repeats, with greater than or equal to 39 CAG repeats resulting in nearly certain development HD within their adult years. The core feature of the disease is involuntary, dance-like movements (chorea). Though several studies have suggested both cognitive and psychiatric manifestations of the disease may predate the onset of motor symptoms (Hahn-Barma et al., 1998; Paulsen, Zhao, Stout et al, 2001), diagnosis of HD is made only when motor symptoms are evident. Testing is now available to determine if the gene is present, giving rise to a group of "prodromal HD" (PreHD) individuals who know they will eventually develop the disease but do not yet evidence motor symptoms.

Those with Huntington's disease are also reported to display an increased prevalence of a wide range of behavioral and psychiatric symptoms, including depression, apathy, irritability,

anxiety, among others (Craufurd, Thompson, & Snowden, 2001; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001; Rosenblatt, 2007). It is estimated as many as 98% of HD patients evidence some psychiatric manifestation (Paulsen, Ready, et al., 2001; Shiwach, 1994). While psychopathology in HD has been proposed to be related to the disease course (Duff, Paulsen, Beglinger, Langbehn, & Stout, 2007), others suggest it is unrelated to direct disease process measures (i.e., motor score and cognitive functioning) and are more variable across patients (Thompson, Snowden, Craufurd, & Neary, 2002). Apathy, however, has been found to be the only psychiatric measure consistently related to progression in prodromal HD and manifest HD, is likely because of loss of frontal functioning (Duff et al., 2010; Van Duijn, Kingma, & Van der Mast, 2007).

Similar to PD, HD is characterized by subcortical basal ganglia degeneration. However, in HD, atrophy of the caudate and putamen are the principle structures that disrupt normal frontal-subcortical dopaminergic networks. Studies have found that both prodromal HD patients close to onset and those with manifest HD patients demonstrate emotional facial recognition deficits (Dogan et al., 2013; Henley et al., 2008; Novak et al., 2012), which are similar to FTD but not as severe as FTD (Snowden et al., 2008). This deficit is present across modalities, with impairment also seen in identifying emotion in vocal expressions (Snowden et al., 2008), inability to portray an emotional expression in HD patients (Trinkler et al., 2013), and difficulty extracting the emotions of others in theory of mind and social cognition tasks (Baez et al., 2015). While HD patients can evaluate valence for stories and scenes appropriately (Ille et al., 2011), they tend to overestimate arousal (de Tommaso et al., 2013), further complicating the ability to identify the specific deficit related to facial processing. The deficit in emotional expression recognition across

modalities suggests that emotional memory, which also utilizes some of the same prefrontal and amygdala networks, may be impaired in HD.

**Changes in the amygdala and prefrontal cortex in HD.** Changes in limbic regions, including the amygdala, occur early in HD and are similar to changes proposed to occur in those with various forms of psychopathology (Petersén & Gabery, 2012). Neuroimaging results are mixed, primarily due to the heterogeneous nature of HD, but suggest compensatory over-activation of the amygdala and under-activation of frontal networks (specifically mPFC) and other emotion-specific regions (Dogan et al., 2013). HD patients demonstrate emotional deficits and evidence decreased functional connectivity between the amygdala and facial processing regions, a change that is also seen in PD (Mason et al., 2015, Lin et al., 2016).

Prefrontal cortical degeneration in HD occurs partially through the loss of innervation from basal ganglia structures. This loss of input from the striatum (i.e., caudate and putamen) results in cell death of prefrontal cortical targets due to depleted frontostriatal networks (Tekin & Cummings, 2002). Specific white matter (WM) atrophy has also been found to occur much earlier in the disease process than gray matter (GM) atrophy, suggesting WM volume loss may be the earliest sign of progression and be related to time until onset (Ciarmiello et al., 2006; Rosas et al., 2006). Additionally, while GM atrophy tends to occur in the areas that receive striatal projections, WM deficits are more wide-spread and likely related to a demyelinating process rather than solely the result of GM degradation (Stoffers et al., 2010). Both PreHD and manifest patients also demonstrate less glucose metabolism in the frontal and temporal cortex and striatum (Ciarmiello et al., 2006). Notably, GM atrophy was not related to number of CAG repeats.

Beyond general WM and GM atrophy, Nopoulos et al. (2010) noted that those near to diagnosis of clinically manifested HD demonstrated hyperactivity of ACC. PreHD individuals also

have been found to evidence decreased OFC activation (and increased amygdala activation) in response to negative feedback relative to controls (Kloppel et al., 2010).

Despite these impairments in prefrontal regions and the amygdala, other aspects of HD make interpretation of emotional recognition deficits difficult. Reasoning for this emotional recognition impairment is next described. However, confounding factors, such as altered perceptual processing in HD, the complexity and inherent arousal of facial expressions, and the relative proportion of positive compared to negative stimuli make interpretations difficult and suggest the need for more controlled look at emotional processes in HD.

### **Theories of emotional facial recognition impairment in HD**

Several hypotheses have been proposed to account for the emotional facial recognition deficits in HD that relate to the current study. First, HD patients are proposed to have deficits in the recognition of specific emotions, contributing to lower recognition for specific emotional facial expressions. Disgust has been proposed to be one of the earliest emotions impaired in PreHD due to specific degeneration of the insula (Dogan et al., 2013), which can be seen prior to motor symptom onset (Johnson et al., 2007). However, these results are inconsistent, with some researchers finding anger to be the most frequently impaired (Henley et al., 2012), while others suggest impairment in several emotions (i.e., anger, fear, and disgust) in HD (Snowden et al., 2008), and still others suggesting a more global impairment for all negative emotion (Speedie, Brake, Folstein, Bowers, & Heilman, 1990; Croft, McKernan, Gray, Churchyard, & Georgiou-Karistianis, 2014). In a meta-analysis, Bora, Velakoulis, and Walterfang (2016) found the largest effect sizes for anger, disgust, and fear, followed by moderate effect sizes for sadness and surprise, and the smallest effect size for happiness. In PreHD, effect sizes moderate for anger, disgust, and



fear, small for sadness, and not significantly different from controls for surprise and happiness. Further analyses in their study suggested: 1) performance was related to fluency, possibly suggesting a relationship with executive functioning, 2) poorer performance was related to increased illness duration, higher CAG repeats, higher motor score, and increased disease burden, and 3) In PreHD, impaired facial recognition suggested increased likelihood of developing motor symptoms within the next five years. Considering these results, the inconsistency of results across studies, and deficits present in other disease models (e.g., FTD, PD), it is unlikely that specific neural regions related to any one emotion are accounting for the deficits seen, but that results are related to a more general emotional processing deficit that progresses to eventually include happiness (Kordsachia, Labuschagne & Stout, 2016). Further, many studies have used only one positive facial expression (i.e., happiness) and often multiple negative expressions (e.g., anger, disgust, sadness, and fear), therefore making it more likely that analysis of negative expressions would result in significant effects. In addition, recognition of facial expressions of happiness are frequently reported to be near perfect performance in healthy controls (e.g., Ekman happy faces = 95% agreement control participants; Ekman et al., 1987) while recognition of facial expressions such as disgust, fear or anger are reported to be much lower (e.g., Ekman faces = 86%, 84%, and 81% agreement, respectively, in control participants; Ekman et al., 1987). This may suggest that negative facial expressions identified above inherently represent more difficult perceptual discriminations when compared to a positive facial expression, such as happiness. In any case, these findings in normal participants certainly suggest a much greater degree of variability in identification of many negative facial expressions.

A second proposal suggests a social cognitive impairment, specifically the inability to interpret stimuli due to impaired “mirroring,” related to deficits in the realm of theory of mind

(Baez et al., 2015). This is supported by poor performance in other emotional domains (e.g., facial expression production and vocal emotional identification) and theory of mind tasks. However, this would not account for good performance on positive facial expressions or the increased performance found on dynamic emotional stimuli (Baez et al., 2015). Additionally, on a task examining empathy, prodromal HD patients do not have deficits in cognitive or emotional aspects (Maurage et al., 2016) despite impairment in emotional facial recognition.

Finally, despite intact facial scanning and non-affective facial matching in some studies (van Asselen et al., 2012), it is suggested that HD patients may have a general visual processing deficit. This is supported by findings that patients have difficulty with visual matching and recognition for items without emotional significance (Lawrence et al., 2000) as well as evidence occipital GM loss and impairment in object information processing deficits (despite intact perception) relative to controls (Wolf et al., 2014). This may account for the difficulties with negative emotions, which require greater distinction among fine details. For example, researchers have observed “anger/disgust confusion,” in which the details of these two emotions are particularly difficult to distinguish, even among controls (Dogan et al., 2013). However, even on much simpler emotional tasks, and those without a visual component (e.g., vocal expressions) HD patients demonstrate continued impairment relative to control groups (Snowden et al., 2008), suggesting emotional facial recognition may be related to an underlying deficit in affective processing.

In summary, emotional recognition deficits have been consistently found in HD despite intact non-affective facial processing reported in some studies. However, researchers have not agreed upon the explanation for this deficit. In relation to other diseases, this impairment is proposed to be greater in manifest HD than PD (Kordsachia, Labuschagne & Stout, 2016), but be

less severe in general in relation to FTD (Snowden et al., 2008). Confounding factors present in facial emotion recognition tasks include the disproportionate amount of negative to positive faces in these tasks and the reliance on visual/perceptual processing, which has been known to be impaired in HD. To date, no studies have examined emotional memory in patients with HD despite the fact that amygdala and prefrontal cortex changes are known to occur in this population. In order to circumvent possible confounding perceptual difficulties with the use of emotional faces, the current study will examine verbal emotional memory, as language abilities remain generally intact in HD (Lawrence et al., 1996). This study will attempt to investigate the degree of impairment in emotion processing by specifically examining emotional memory in HD and its relationship to disease characteristics, facial emotion recognition, executive dysfunction, and apathy.

### **Purpose of the Current Study**

Prior research suggests that immediate emotional memory enhancement, in the absence of high arousal, is more strongly associated with prefrontal cortex activation (Kensinger & Corkin, 2004; LaBar & Cabeza, 2006), while highly arousing material is primarily influenced by limbic regions (Hamann, 2001). Within disease models, impairment of emotional memory is found in both FTD (with impaired PFC and intact amygdala; Kumfor et al., 2013) and those with bilateral amygdala lesions (with intact frontal cortices; Hermans et al., 2014), demonstrating the importance of both regions in emotional processing and memory.

In Huntington's disease, neuroimaging studies suggest compensatory over-activation of the amygdala and under-activation of frontal networks and other emotion-specific regions (Dogan et al., 2013). Manifest Huntington's disease patients have been proposed to have specific deficits

in emotional processing, most consistently demonstrating impairment recognizing and identifying emotional facial expressions (Dogan et al., 2013; Henley et al., 2012; Snowden et al., 2008). Some have argued that this could be accounted for by basic perceptual processing deficits when making fine visual discriminations (Lawrence et al., 2000; Wolf et al., 2014). Although perceptual processing likely impacts results, HD patients also demonstrate impairment in emotional recognition when presented with dynamic facial expressions and vocal expressions, which are less reliant on fine visual discrimination (Baez et al., 2015). Additionally, prodromal individuals demonstrate lower performance on emotion facial recognition tasks long before motor symptom onset (Novak et al., 2012), which has led some authors to suggest that misidentification of emotional faces may be an early indication of disease onset. Further, emotional memory and emotional facial identification are suggested to use some of the same initial processing networks, specifically involving assignment of value/significance (Rolls, 2015), linking of emotion to conceptually related knowledge (Adolphs, 2002), and interaction and integration of limbic and cortical regions (Phan et al., 2002; Phillips et al., 2003). Performance on executive function tasks has also been found to be related to performance on emotional facial expression identification tasks in FTD but not performance in other cognitive domains, such as language, memory, and visual tasks (Snowden et al., 2008). Likewise, executive function has been proposed to be the primary factor in determining if emotional memory enhancement will be found in neurodegenerative disease models (Broster et al., 2012; Borg et al., 2011). To date, no study has investigated emotional memory in manifest or prodromal Huntington's disease patients.

The purpose of this study is to examine emotional memory in HD and its relationship to the disease process, including disease progression, executive dysfunction, and apathy. This study will use verbal stimuli to limit the confounding effects of fine detail discrimination or

visuoperceptual processing that may impact emotion recognition results. Specifically, immediate recall and recognition of pleasant, unpleasant, and neutral affective words (equated on arousal) was examined in healthy controls, prodromal HD (PreHD) patients, and manifest HD patients. Notably, valence has been found in PD patients to be influenced by dopaminergic systems (Hälbig et al., 2011). Given the neurological changes that occur during the course of the disease, including changes in amygdala and prefrontal function, it is predicted that HD patients will not benefit from an emotional memory enhancement relative to controls or PreHD patients. It is also predicted that, since these changes occur on a continuum, PreHD patients may also demonstrate significantly different emotional memory from controls, likely demonstrating a reduced enhancement effect. To examine changes over the course of disease, both motor exam score and burden of pathology (Age x (CAG-35.5); Dogen et al., 2013; Penny et al., 1997) will be used. Motor exam score, as noted above, is used to diagnose HD and typically increases as the disease progresses, likely due to the dysregulation of the nigrostriatal pathway. Burden of pathology, or disease burden, reportedly quantifies the lifelong exposure to the disease and has been found to be related to rate and distribution of neutral atrophy, with higher CAG burden related to more WM atrophy (Hobbs et al., 2010), the rate of progression (Rosenblatt et al., 2006), and the clinical manifestations of HD (Sánchez-Pernaute et al., 1999), though CAG repeat was not found to be related to motor score (Rosenblatt et al., 2006). Further, months of disease exposure will be used. Specifically, this metric will take into account manifestation and will allow for a continuous estimation of months away from manifestation in prodromal HD. Months until diagnosis will be estimated in the prodromal group using a formula suggested by Zhang et al. (2011;  $\text{years to diagnosis} = \exp(4.4196 - 0.0065 \times (\text{Age} \times (\text{CAG} - 33.6600)))$ ), while for manifest patients, months will be used since diagnosis (i.e., presence of motor symptoms) based on chart review or self-report. Participants completed

executive functioning tasks (inhibition, working memory, set shifting), due to the model of emotional memory in neurodegenerative diseases in executive functioning is predicted to determine benefit or decrement in emotional memory (Broster et al., 2012). Additionally, participants will complete a questionnaire to assess motivation (i.e., apathy) given the relationship with progression and involvement of the mPFC (Duff et al., 2010; Van Duijn, Kingma, & Van der Mast, 2007). Lastly, participants will complete an emotion facial recognition task to directly compare their performance on emotional verbal memory to emotional facial recognition, which past research suggests is typically impaired in HD (Snowden et al., 2008).

### **Objectives and Hypotheses**

- 1) To investigate the overall ability of Huntington's patients and PreHD individuals to benefit from emotional memory enhancement relative to control participants

Hypothesis 1a. Prodromal HD patients will demonstrate a decreased emotional memory enhancement relative to controls (i.e., while emotional words will be remembered more than neutral in PreHD patients, relative to controls participants, PreHD patients will still evidence significantly lower proportion of emotional words recalled and less accurate recognition for emotional words relative to neutral).

Hypothesis 1b. Overall, HD patients will fail to demonstrate an emotional memory enhancement (i.e., relatively equal word memory across negative, positive, and neutral categories) compared to the PreHD and control individuals (who will evidence better memory for positive and negative relative to neutral words) in both proportion of emotional words recalled and recognition accuracy.

2) To investigate the relationship of disease severity (i.e., motor score) and burden of pathology (using the formula:  $\text{Age} \times (\text{CAG} - 35.5)$ ; Dogen et al., 2013; Penny et al., 1997) in PreHD and HD individuals in relation to emotional memory. Both will be examined because although motor score is a standard clinical measure of disease progression, it can be influenced by dopaminergic medication, while burden of pathology examines lifetime disease exposure.

Hypothesis 2a. As motor score increases (i.e., more prominent motor symptoms are present), patients will have more difficulty recalling and recognizing emotional words relative to neutral.

Hypothesis 2b. In HD and PreHD patients, as estimated disease burden increases (related to age and CAG repeats), patients will have more difficulty freely recalling and accurately recognizing emotional words relative to neutral words.

3) To examine the relationship between emotional memory enhancement and ability to recognize emotional facial expressions

Hypothesis 3. Better performance on an emotional facial recognition task (i.e., higher mini-SEA emotion recognition performance) will be positively correlated with increased proportion recalled and more accurate recognition of emotional words relative to neutral.

4) To examine the relationships of executive function and apathy to emotional memory enhancement (i.e., higher negative and positive recall and recognition relative to neutral words)

Hypothesis 4a. Better executive function performance, as measured through a composite of executive function measures, will be positively correlated with enhanced emotional memory (proportion of emotional words recalled relative to neutral, recognition accuracy of emotional words relative to neutral).

Hypothesis 4b. Greater apathy (higher AES-Self Total score) will be negatively correlated with recall and recognition accuracy of emotional words relative to neutral (i.e., evidence decreased proportion recalled and recognition accuracy for emotional words).



## METHODS

### Participants

A total of 81 participants were included in the analyses for this study with 55 patients recruited with the HD gene. Groups consisted of control participants (n=26), prodromal HD patients (n=26), and manifest HD patients (n=29). All participants were required to be between the ages of 18 and 65, with English as their first learned and primary language, and with normal or corrected vision. Participants were not eligible if they had ever had a psychotic episode, were actively intoxicated or using substances by self-report (cocaine, amphetamines, barbiturates, benzodiazepines, opioids), had a neurological disease (other than Huntington's disease for the HD groups), and were unable to physically or cognitively to complete any of the study procedures. Additionally, each group required more specific inclusion and exclusion criteria. Manifest HD patients required either a genetic test that confirmed presence of HD gene or a family history of HD and clinically manifested motor symptoms (with 100% Diagnostic Confidence Level, equivalent to a score of 4, based on the Motor Scale of the UHDRS as diagnosed by a neurologist), without juvenile onset (i.e., motor symptoms began before 18 years old). Due to the complexity of the computer task, patients were required to be relatively early in the disease process to ensure cognitive ability to complete the task. This was assessed based on past MoCA score (brief cognitive screener; see materials section), self-reported functional status, and score on the Total Functional Capacity (TFC) scale, which offers a rough estimate of functional status. On the TFC, patients were required to live relatively independently with help only on more complex IADL (TFC>8, which may include inability to work and manage finances, but includes ability to continue

to perform household chores, complete ADLs, and be cared for at home). For the prodromal HD group, patients must have been genetically tested and determined to be gene positive for the HD gene (CAG repeats greater than or equal to 39) without ever having a motor exam that indicated they had manifested HD motor symptoms with a 100% Diagnostic Confidence Level (i.e., score of 4 indicating patient met the criteria for clinical diagnosis of HD). Both groups required that patients can provide his or her own consent. Capacity to consent was determined by MoCA total score at the time of the visit (or within the last four months) at 22 or above. If a score of 22 was not achieved, specific methodology was used to establish capacity (Appelbaum & Grisso, 1988; Berghmans, 2001; Karlawish et al., 2013). See Appendix A for detailed procedure. Additional questions to establish the ability to consent were administered to six prodromal HD patients and ten manifest HD patients. Controls participants were not administered the MoCA.

Those in the control group were not allowed to be at risk for developing HD (i.e., family history with unknown disease status), and were ineligible if they were taking medications that might affect emotional processing (e.g., benzodiazepines, beta blockers, neuroleptics, selective serotonin reuptake inhibitors, and tricyclic antidepressants) or if they were receiving treatment for psychiatric disorder (e.g. major depressive episode, manic episode, panic disorder, or panic attacks) at the time of the study. HD participants were not excluded due to psychiatric disorders as there is a high prevalence of psychiatric disorders in HD (as high as 98% as noted above; Paulsen, Ready, et al., 2001; Shiwach, 1994). Control participants were used to establish the expected pattern of results without the impact of psychiatric disorder.

**Recruitment.** IRB approval for human subjects recruitment was obtained (Appendix B). Full recruitment process is detailed in Figure 1. Diagnosed HD and PreHD patients were recruited from the USF HD Center of Excellence (HDCE). Recruitment occurred via telephone or in person.

Individuals were primarily identified through the Huntington's Disease Registry, which serves as a database of basic demographic and disease related variables. Voluntary participation in the HDCE registry had previously been obtained for patients via written consent in which participants consented to be contacted about future research studies. Additional participants were identified through Enroll-HD (an observational study with yearly visits, though these individuals are likely part of the registry), as this study also allows for participants to be approached for other studies. Lastly, recruitment also took place within the HD clinic.

Once a patient was identified, patients were invited to participate. If they agreed to participate, a time for the study visit was arranged, typically co-occurring with their clinic or research visit to reduce any burden of travel. All individuals were assured that their decision to participate in the present study did not impact their clinical care. In addition, all individuals were assured that the data collected during their study participation would not be included in their medical record. Control participants were recruited through two methods: 1) through family members or other individuals who accompanied participants to the study and met the above criteria, or 2) through an undergraduate research participation system (SONA) at University of South Florida in which participants received research credit for psychology courses. Within the control participants, 12 were family members and 14 were recruited through SONA.

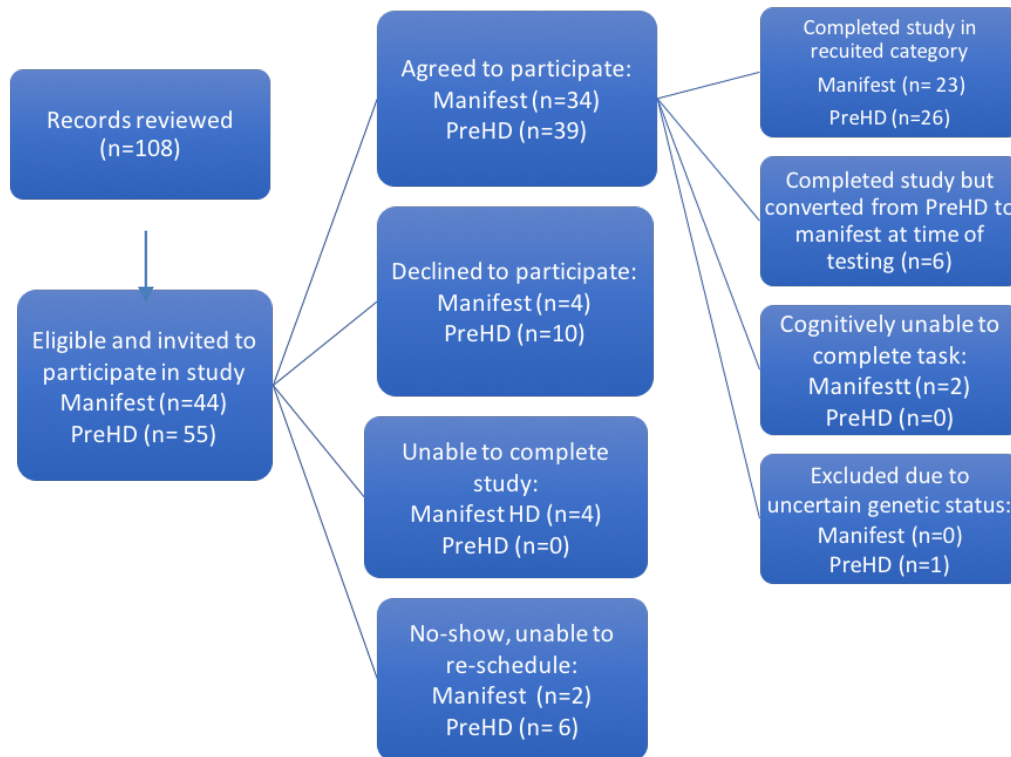


Figure 1: Recruitment flow chart for prodromal and manifest HD patients. Unable to complete study consisted of subjects with too much motor impairment, not wishing to complete testing at the time of the study visit, or who did not complete due to time constraints.

## Materials

**Demographics Questionnaire.** Demographics were obtained from the HDCE Registry or the Enroll study, when possible, to reduce participant burden or directly from the patient. Data obtained included: basic demographic variables (age, sex, years of education), disease history (CAG repeats, date of diagnosis, most recent motor score (within 6 months), recent Total Functional Capacity, current medications, and psychiatric history. The formula  $\text{Age} \times (\text{CAG} - 35.5)$  was used to calculate burden of pathology for each HD and prodromal HD participant for

whom CAG repeats were available (Dogen et al., 2013; Penny et al., 1997). A total of 51 out of 55 participants had available CAG repeat data and were included in these analyses. Additionally, a formula from Zhang et al., 2011 was used to determine years until onset in the prodromal HD patients, with the formula of Years to diagnosis =  $\exp(4.4196 - 0.0065 \times (\text{Age} \times (\text{CAG} - 33.6600)))$ . This calculation was used with patient's report of date of onset of motor symptoms to create a continuous variable, with prodromal patients having negative estimated months until diagnosis and manifest patients having positive estimated months since diagnosis.

**Apathy Evaluation Scale – Self version (AES-S;** Marin, Biedrzycki, & Firinciogullari, 1991). The AES-S is an 18-item self-report measure in which the individual rates how much a set of statements describe his or her thoughts, feelings, or actions. As such, three subscales are derived that contain items specifically identifying apathy related to cognition, behavior, and emotion. Items are rated as applying not at all, slightly, somewhat, or very/a lot with total scores ranging from 18 (no apathy) to 72 (high apathy). The AES-S has been found to have adequate discriminant validity, convergent validity, internal consistency ( $\alpha = 0.86$ ) with test-retest reliability of ( $r = 0.76$ ) (Marin, Biedrzycki, & Firinciogullari, 1991).

**Mini-Social Cognitive Emotional Assessment (Mini-SEA;** Bertoux, Funkiewiez, O'Callaghan, Dubois, & Hornberger, 2013). The Mini-SEA contains a 10-item version of the Faux-Pas test (Stone et al., 1998) with pictorial representations and a facial emotion recognition test using 35 of the standardized Ekman faces (1975), with 5 expression of each category (neutral, happiness, surprise, disgust, anger, fear, and sadness). Only the facial recognition portion of this measure was used. This test is proposed to be sensitive to mPFC damage, particularly ventromedial prefrontal damage evidenced in bvFTD (Bertoux, et al., 2012, Bertoux et al., 2014). Performance on the Mini-Sea was able to distinguish bvFTD (with significant vmPFC damage) from AD in

greater than 82.5% of cases and bvFTD from older controls in 88% of cases, with facial recognition being more impaired than faux pas performance in bvFTD (Bertoux et al., 2013).

**Affective stimuli.** Words were taken from the Affective Norms for English Words (ANEW) which provides average valence, arousal, and frequency ratings (Bradley & Lang, 1999). ANEW normative ratings for the combined male and female norms were used. A total word bank of 24 of each positive, negative, and neutral words was created, with each category equated on valence, arousal, frequency, and word length (See Appendix D for piloting procedures). From this word bank, three pseudorandomized lists were created, with each list containing 36 target words (12 positive, 12 negative, and 12 neutral words), with the remaining words from the bank used as lures in the recognition trial. Three pseudorandomized word lists are needed so that word lists remain equated in valence, arousal, semantic relatedness, frequency, and word length, which is unlikely to occur if word lists were randomly generated. For each created list, four buffers total (neutral valence, high frequency) were used in the beginning and end of the list to account for primacy and recency effects. Participants were randomly assigned to a word list and the order in which the words are viewed was randomized by the computer. Participants first viewed the list and categorized each word as “Pleasant,” “Neutral,” or “Unpleasant” (See Appendix C for directions). After a 120 second delay (in which a distractor task consisting of a facial discrimination task of nonaffective faces was administered), participants performed a free recall task, followed by a yes/no recognition task. In the recognition task, lures and targets were mixed and presented in a random order by the computer. Lastly, participants rated the valence of each word on a continuum using a rating scale (Self-Assessment Manikin; SAM) used to create the original normative data set (i.e., the ANEW methodology; Bradley & Lang, 1999).

*Valence and arousal:* All words in the ANEW normative dataset have been rated using the same scale of 1 to 9, with 1 representing either the most negative or lowest arousal and 9 representing the most positive or highest arousal. All valence categories demonstrated statistical significance between them (e.g., positive valence was significantly different from neutral and negative). All categories were equated in arousal (i.e., not statistically different), meaning that arousal is not expected to differentially influence recall and recognition of words across the three valence conditions.

*Frequency:* Frequency was equated across category and within list based data made available by Brysbaert and New (2009), who sought to update and improve upon the frequently used Kucera and Francis frequency data (Francis & Kucera, 1982). All ANEW words were represented in the normative data and normative data is publically available from:

<http://brm.psychonomic-journals.org/content/supplemental>.

*Semantic relatedness:* Latent Semantic Analysis measured by matrix comparison was used to evaluate semantic relatedness within category and within lists. This method has been suggested to be the best method for evaluating semantic relatedness, which has been suggested to be the most appropriate way to estimate word relatedness (Grider & Malmberg, 2008; Landauer, Foltz, & Laham, 1998), instead of having individuals rate the perceived relatedness of word pairs (Talmi & Moscovitch, 2004) or using Internet search engines (Buchanan, Tranel, & Adolphs, 2006). An online resource (<http://lsa.colorado.edu/>) was used to determine semantic relatedness, using matrix term-to-term comparison with “up to first year of college general reading” as the semantic space.

**Montreal Cognitive Assessment** (MoCA; Nasreddine et al., 2005). The MoCA is a brief (approximately 10 minutes) cognitive screening measure with items assessing eight domains,

including visuospatial/executive, attention, naming, language, abstraction, memory/delayed memory, and orientation. The maximum score is 30 points, with 22 points a suggested cut-off for evaluating for capacity for consent (Karlawish et al., 2013). In PD patients, the MoCA was strongly correlated with the Mini Mental State Exam ( $r = 0.66$ ) and a neuropsychological battery ( $r = 0.72$ ), demonstrating good convergent validity (Gill et al., 2008). In these same patients, the MoCA demonstrated adequate test-retest reliability over 133-day period ( $ICC = 0.79$ ), with a mean change of 0.50 points between the two testing intervals, and good interrater reliability ( $ICC = 0.81$ ; Gill et al., 2008).

**Stroop Color and Word Test** (Golden, 1978). This measure assesses executive function, specifically aspects of inhibition, selective attention, and cognitive flexibility. The Stroop requires individuals to complete three related tasks. In the first task, names of colors are read aloud as quickly as possible until completion of the stimulus page. In the second task, the participant is presented with colored X's and must name color of ink as quickly as possible. In the final task, the participant is presented with names of colors printed in a different ink color and are required to say the color of ink a word is printed in. The participant is required to inhibit the overlearned response of reading the word and instead must just say the color of the ink (e.g., the word blue may be printed in red ink and the individual must say "red"). Test-retest has not been found to be significantly different between one and two week intervals, with overall test-retest reliability for Word ( $r = 0.83$ ), Color ( $r = 0.74$ ), and Color-Word ( $r = 0.671$ ) comparable to other investigations with alternative forms (Frazen, Tishelman, Sharp, & Friedman, 1987). Additionally, neuroimaging data has supported that the interference (Color-Word) portion of the Stroop task activates medial prefrontal areas (Stuss et al., 2001) and the ACC (Ravnkilde et al., 2002).



**Trail Making Test** (*TMT-A and TMT-B*; Reitan & Wolfson, 1985). This commonly used test from the Halstead-Reitan Battery is designed to measure psychomotor speed and visual scanning. In TMT-A, participants are required to quickly connect numbers spread about a page in sequential order. In TMT-B, participants are additionally required to maintain and shift response sets. The participant is asked to connect a series of circles on a page sequentially, alternating between numbers and letters. Construct validity evaluation of this test suggests that TMT-A indexes visuoperceptual abilities while TMT-B indexes working memory and set-shifting, with a calculation of B-A representative of executive ability (Sanchez-Cubillo et al., 2009). When given a day apart, performance on TMT-A ( $r = 0.87$ ) and TMT-B ( $r = 0.86$ ) have demonstrated good reliability, with a coefficient of repeatability of 8 and 22 seconds, respectively (Amodio et al., 2002).

**Wechsler Adult Intelligence Scale, Fourth edition, Digit Span Subtest** (Digits; Wechsler, 2008). This measure was also used during the distractor portion of the study. Digits measures basic attention and working memory. It is divided into three portions (forward, backward, and sequencing) that require repetition and manipulation of numbers. Digit Span is a subtest within the Wechsler Adult Intelligence Test Scale – Fourth Edition. Participants are read a series of numbers and are asked to first repeat them as they were heard, which is generally considered a basic attention task (Kaufman, McLean, & Reynolds, 1991). Next participants hear different numbers and say them in the backwards order, which is generally considered a working memory task (Black, 1986; Banken, 1985). Lastly, participants complete a more difficult working memory task and are given a string of numbers and asked to say them in ascending numerical order. Internal consistency has been shown to be adequate in both the overall Digits Span score ( $\alpha = 0.93$ ) as well as the Forward ( $\alpha = 0.81$ ), Backwards ( $\alpha = 0.82$ ), and Sequencing

( $\alpha = 0.83$ ) portions (Wechsler, 2008). Average test retest reliability has also reported to be good for the overall subscale ( $r = 0.82$ ) as well as the Forward ( $r = 0.74$ ), Backwards ( $r = 0.69$ ), and Sequencing ( $r = 0.70$ ) portions (Wechsler, 2008). Imaging studies have indicated the involvement of prefrontal regions, including the DLPFC and ACC with both forward and reverse (Gerton et al., 2004).

**Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1989).** This test is a measure of verbal fluency, cognitive flexibility, and semantic knowledge. Alternate forms exist. Participants are given three one-minute trials to generate words that begin with a given letter as quickly as possible. Three letter cues are given (F, A, and S). The test is scored based on the total number of words generated. When using PET scans, FAS has been found to be a good measure of prefrontal function, demonstrating activation in the inferior frontal, DLPFC regions, and ACC among other regions (Ravnkilde et al., 2002). Test retest reliability has been reported to be highly correlated ( $r = 0.79$ ) with a one week interval between testing sessions (Duff, 2014).

**Control word task.** To ensure that participants were providing good effort and that results were not due to cognitive factors alone, a control word memory task was created with a known effect, with studies consistently finding low frequency words are more accurately recognized than high frequency items across several studies (Rugg, Cox, Doyle, & Wells, 1995; MacLeod & Kampa, 1996; see Appendix E). Using the same frequency measure as the affective word lists, *SUBTLWF* was used, which provides the word frequency per million words in this database with a word corpus of over 51 million words (Brysbaert & New, 2009). The word list used consisted of ten high frequency words with frequencies above 100 per million (consistent with DeLosh et al., 1996), ten low frequency at less than 3 per million (consistent with Balota et al 1980), and 20 middle frequency words between 20 and 35 per million as lures. Recognition was used as a

measure of the frequency effect, however, free recall was included to match the methodology of the emotional memory task.

**Control facial task.** A control facial task was used as the distracting task between encoding and recall/recognition of the primary experimental emotional memory task. This control facial task was taken from the Florida Affective Battery (Bowers, Blonder, & Heilman, 1991). It consists of pages with two women's faces without external cues such as jewelry, hairline, etc). Two practice items were shown with feedback provided if incorrect. For each of the twenty test items, the participant responds "same" or "different" to indicate if the faces were of the same person or different people, with half of trials consisting of a correct same response and half of correct different responses. This facial task was also used as a control measure to examine the most basic facial recognition discrimination task, which is expected to be maintained in Huntington's disease (Snowden et al., 2008). In the current study, the entire sample could correctly identify an average of 19.16 (SD=1.41) faces.

## **Procedure**

Capacity to consent was assessed (HD and Prodromal HD only) and informed consent was obtained for all participants. All stimuli were administered on a MacBook Pro laptop computer using PsychoPy (Peirce, 2007, 2009; Peirce et al., 2011). Words were presented centrally, in white, Arial font (letter height = 0.15) with default gray background. Participants were shown the list of 36 words (12 in each category: pleasant, neutral, unpleasant, with 4 total buffers) and asked to categorize each word as "Pleasant, neutral, or unpleasant" (See Appendix C for full task directions). Each word was exposed for a set amount of time and the participant was required to make his or her rating in that time or the computer automatically moved to the next item. Due to

slowed processing speed in HD, controls were presented each word for 2 seconds (with a 0.1s ISI), Prodromal HD for 3 seconds, and HD patients for 4 seconds. Exposure times were investigated for controls, then increased for HD due to decreased processing speed beginning in prodromal manifest HD (Maroof, Gross, & Brandt, 2011) and continuing into manifest HD (Paulsen, 2011). Exposure times were then piloted to establish the suitability for the current population (see Appendix D). On average, participants failed to respond (i.e., missed) 0.99 (SD=2.00) items during the encoding task. Groups were not significantly different on the number of items missed ( $H(2) = 1.69$ , n.s.), with the control group missing an average of 1.08 (SD=1.23) items, prodromal HD missing 1.08 (2.81), and manifest HD missing 0.83 (SD=1.75). Participants were not informed of the memory task, but debriefed at the end of the study.

Participants then engaged in a 120-second distractor using a facial discrimination test of unaffactive faces (i.e., control facial discrimination task). After the distractor, participants were given a free recall task with three minutes allowed for recall, followed by a yes/no recognition computer task. On this trial, participants were asked to indicate whether words were previously presented, with “yes” indicating a word was previously seen and “no” indicating a new word that was not seen before. They then rated if they were confident (yes) or unconfident (no). After the recognition trial, participants rated the valence of all 36 words (i.e., targets and lures) on valence using a 9 point Likert with a pictorial Self-Assessment Mannequin (SAM; Bradley & Lang, 1994), consistent with the methodology of Bradley and Lang (1999) and Warriner et al. (2013). Next, participants completed all questionnaires cognitive tests except for the COWAT. Lastly, the control word task was administered. In this task, 10 high frequency and 10 low frequency words were presented on the screen in a randomized order using the same time exposure as the emotional memory task (i.e., 2, 3, and 4 seconds, based on group). Participants were asked to “read each

word aloud and try to remember it.” After a short distraction task (counting backwards for 30 seconds), participants were given a recall and recognition task.

**Scoring and calculation of data.** D prime ( $d'$ ) was used as a measure of recognition sensitivity. Sensitivity analysis provides a way to examine recognition (i.e., signal) while also considering how susceptible the individual was to false alarms of the same valence category (i.e., noise) and calculates the difference in standard deviation units (Stanislaw & Todorov, 1999). Calculation of  $d'$  includes using hits as the proportion of items correctly recognized of total words per category (i.e., twelve) and calculating a similar proportion for lures. The z- scores of both hits and false alarms were calculated, and then false alarms were subtracted from hits. Therefore, the larger the  $d'$  value, the better discrimination and recognition of the words.

Table 1: Correlation among executive functioning measures used for composite score

Variable	Trails B T	Stroop CW T	Digit-SS	FAS-T
Trails A T	0.84	0.65	0.47	0.52
Trails B T	--	0.64	0.45	0.58
Stroop CW	--	--	0.43	0.45
Digit SS	--	--	--	0.50
FAS T	--	--	--	--

Note: \*all measures correlated at  $p < 0.01$

To calculate executive functioning composite score, z scores were calculated for each measure and added together to form a composite score (Ackerman & Cianciolo, 2000).

Correlations among the cognitive measures were examined, consistent with the recommendations of Ackerman and Cianciolo (2000), who suggest that to create a composite score, the variables should be highly correlated to ensure they are assessing the same domain. In the current study, correlation coefficients between executive function variables ranged from 0.45 to 0.84, with all measures significantly correlated at  $p < 0.01$  (Table 1).

**Data Diagnostics.** Data was examined using IBM SPSS 24 for Mac. All analyses were investigated with free recall (difference between affective and neutral proportion recalled only) and corrected recognition rates ( $d'$ ; within affective category and difference between affective and neutral). For emotional memory enhancement, neutral values were subtracted from affective values, such that higher values indicate emotional enhancement. All data was examined as it was used in analyses, such that all emotional memory variables were examined by group (i.e., control, prodromal HD, and manifest HD; Table 2), and by grouping all HD patients (i.e., prodromal and manifest HD together; Tables 3a-e). Variables were first inspected for outliers using boxplots. Given low rates of free recall (i.e., one or zero items), three participants were excluded from free recall analyses for low recall as these values represented statistical outliers. A further correction involved two outliers when examining overall participant data. These were addressed by making the maximum value for  $d'$  (i.e., all targets and no lures) slightly lower across all groups and conditions (i.e., 4.65 changed to 4.23) as these values were artificially inflated based on the calculation of  $d'$  using z-scores with approximate numbers for 0 and 1. Variables were also assessed for skewness and kurtosis, with a criterion of  $z = 1.96$  used to establish significant skew or kurtosis. Lastly, normality was examined using the Shapiro-Wilk test in SPSS. Variables that could be transformed include PHQ and AES, while motor score and emotional facial recognition were unable to be corrected with transformations. Due to multiple variables with the same rank (i.e., zero occurring in 11 patients) and nonparametric properties that could not be normalized with a transformation, motor score was analyzed using Kendall's tau.

Table 2: Diagnostics and means of dependent variables by group

Variable		Mean (SE)	Skew	Kurtosis	Normality
Pleasant d'	Control	3.09 (0.13)	0.20	-0.075	n.s.
	Prodromal	2.56 (0.17)	-0.48	-0.53	n.s.
	HD	2.00 (0.19)	0.26	-0.69	n.s.
Neutral d'	Control	2.75 (0.16)	0.21	-0.67	n.s.
	Prodromal	2.51 (0.17)	0.36	-0.60	n.s.
	HD	2.23 (0.19)	0.29	0.35	n.s.
Unpleasant d'	Control	2.81 (0.12)	0.21	-1.00	n.s.
	Prodromal	2.63 (0.20)	0.19	-0.53	n.s.
	HD	1.7 (0.15)	-0.06	-0.042	n.s.
Pleasant recall proportion	Control	0.41 (0.036)	0.17	-0.066	n.s.
	Prodromal	0.32 (0.036)	-0.50	-0.57	n.s.
	HD	0.42 (0.052)	0.51	0.32	n.s.
Neutral recall proportion	Control	0.35 (0.027)	0.35	-0.16	n.s.
	Prodromal	0.43 (0.038)	1.00	1.66	P = 0.044
	HD	0.30 (0.044)	0.29	-0.87	P = 0.025
Unpleasant recall proportion	Control	0.24 (0.025)	-0.015	-0.026	n.s.
	Prodromal	0.25 (0.031)	0.40	0.53	n.s.
	HD	0.28 (0.045)	0.86	1.41	P = 0.005

Note: Skew SE = 0.456, Kurtosis SE = 0.887

Table 3a: Combined HD patient disease characteristics diagnostics

Variable	Mean (SE)	Range	Skew	Kurtosis	Normality
Burden of Pathology	313.60 (13.60)	115.5 – 525	-0.18	-0.52	n.s.
Months to Diagnosis	-38.18 (14.33)	-317 – 137	-0.60	-0.13	n.s.
Motor Score	14.44 (1.83)	0-48	0.92	-0.022	p < 0.001

Note: Motor score cannot be made normal due to several scores of zero; HD group represents both prodromal and manifest HD patients.

Table 3b: HD group recognition diagnostics

Variable	Mean (SE)	Skew	Kurtosis	Normality
d' Pleasant	2.26 (0.13)	-0.13	-0.90	n.s.
d' Neutral	2.37 (0.13)	0.33	0.174	n.s.
d' Unpleasant	2.17 (0.15)	0.44	-0.03	n.s.
d' (P-N)	-0.08 (0.12)	0.17	-0.34	n.s.
d' (U-N)	-0.19 (0.15)	0.34	0.52	n.s.

Note: P-N = Pleasant minus neutral (with higher numbers indicating more emotional memory); U-N = unpleasant minus neutral (with higher numbers indicating more emotional memory); HD group represents both prodromal and manifest HD patients.

Table 3c: HD group free recall diagnostics

Variable	Mean (SE)	Skew	Kurtosis	Normality
Recall P-N	0.034 (0.056)	0.34	0.46	n.s.
Recall U-N	-0.10 (0.04)	0.10	-0.52	n.s.
Pleasant Recall proportion	0.39 (0.03)	0.57	1.17	p=0.004
Neutral Recall proportion	0.36 (0.03)	-0.02	-0.61	p =0.033
Unpleasant Recall proportion	0.25 (0.04)	0.11	-0.82	p= 0.012

*Note:* P-N = pleasant minus neutral (with higher numbers indicating more emotional memory); U-N = unpleasant minus neutral (with higher numbers indicating more emotional memory); proportion recalled is proportion of responses that belonged to that affective category such that 2 of 5 total responses would be 40% recall in that category; HD group represents both prodromal and manifest HD patients.

Table 3d: HD group executive functioning variables

Variable	Mean (SE)	Skew	Kurtosis	Normality
Trails A T	42.77 (2.26)	0.03	-0.45	n.s.
Trails B T	41.49 (2.24)	0.17	-0.31	n.s.
Stroop CW	43.42 (1.45)	0.11	-0.94	n.s.
Digit SS	8.09 (0.33)	0.36	-0.057	n.s.
FAS T	41.07 (1.63)	-0.04	-0.79	n.s.
Composite Score	0.04 (0.56)	-0.19	-1.04	n.s.

*Note:* HD group represents both prodromal and manifest HD patients.

Table 3e: HD group depression and apathy measure diagnostics

Variable	Mean (SE)	Range	Skew	Kurtosis	Normality
PHQ-9	7.85 (0.92)	0-24	<b>0.78</b>	-0.40	<b>p=0.003</b>
PHQsqrt	2.74 (0.16)		0.19	-0.96	n.s.
AES	33.95 (1.54)	18-64	<b>0.82</b>	0.28	<b>p=0.006</b>
AES lg(10)	1.51 (0.02)		0.11	-0.55	n.s.

*Note:* HD group represents both prodromal and manifest HD patients. Variables were transformed as noted.

Specific analyses also required certain assumptions be tested. For Hypothesis 1, a mixed two-way ANOVA was intended to be conducted to examine differences between participants (i.e., across diagnostic group) and within participants (i.e., valence). The assumption of homogeneity of covariance was met, as determined by Box's test of equality of covariance matrices ( $p = 0.29$ ). The assumption of sphericity was met, evidenced by an insignificant value of Mauchly's test



( $p=0.46$ ). However, Levene's test of equality of variances indicated that  $d'$  for unpleasant words was significant (i.e., demonstrated different variances across groups), and therefore the test was unable to be used due to violations of this assumption. However, assumptions were met for use of a one-way ANOVA with a between factor of Group (HD, Prodromal HD and Control) and a one-way repeated measures ANOVA with a within subject factor of Valence (pleasant, unpleasant, neutral).

Supplementary analyses were conducted using regression analyses. For both regression analyses performed (prediction of pleasant and unpleasant recognition sensitivity), data evidenced linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.31 (or pleasant regression) and 1.75 (for unpleasant regression), which is within acceptable limits with predictors and samples size ( $1.53 > d < 2.17$ ; Savin & White, 1977). There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1,  $VIF < 10$ . There were no studentized deleted residuals greater than  $\pm 3$  standard deviations, no leverage values greater than 0.2, and values for Cook's distance above 1. Therefore, assumption of normality of errors was met, as assessed by Q-Q Plot.

A sample size of 75 was determined *a priori* through a power analysis to be the total number of individuals (i.e., 25 per group) needed to detect a small to medium effect size ( $f=0.15$ ) within group. This sample size is also appropriate to detect an effect size of small to medium effect size ( $f=0.17$ ) in a Repeated Measures within-between interaction.

## RESULTS

Demographic variables for each group can be found in Table 4. Groups did not significantly differ in age, education, gender, or depressive symptoms as reported on the PHQ-9. The prodromal HD group and manifest HD group were significantly different in disease related measurements (i.e., burden of pathology, months of HD, motor score), as would be expected. The manifest HD group reported significantly more apathy than both the control, and prodromal HD group. While use of antidepressants was an exclusion for control participants, 18 prodromal HD and 20 manifest HD patients were using antidepressants or anxiolytics. Additionally, 8 manifest HD patients were taking medications often prescribed for chorea (i.e., risperidone, Seroquel, klonopin), with one prodromal HD participant also taking one of these medications for psychiatric reasons (no indication of prior motor symptoms). Motor exam was performed for most participants on the day of testing (n=47).

Table 4: Demographics by group

	<b>Control (n=26)</b>	<b>Prodromal HD (n=26)</b>	<b>Manifest HD (n=29)</b>
Age	39.23 (12.96)	44.46 (11.99)	46.59 (9.86)
Education (yrs)	14.65 (1.41)	14.42 (2.67)	14.27 (2.34)
Gender (M:F)	10:16	6:20	10:19 <sup>c</sup>
MoCA	NA	26.43 (2.92)	22.18 (5.45) t
Burden of Pathology	NA	257.80 (84.21)	378.80 (70.95) t
Months of HD	NA	-130.08 (77.03)	44.21 (43.89) <sup>t</sup>
Motor Score	NA	4.04 (4.80)	23.76 (12.00) <sup>t</sup>
PHQ-9 Total	4.38 (4.35)	7.27 (6.85)	8.38 (6.87)
AES Total	28.38 (8.22)	29.58 (8.28)	37.86 (12.52) <sup>t+</sup>

<sup>+</sup> Manifest HD group significantly different from both prodromal HD ( $p < 0.05$ ) and control groups ( $p < 0.01$ ); <sup>t</sup> Manifest and prodromal HD significantly different,  $p < 0.001$ ; Values provided as mean (SD); <sup>+</sup> Nonparametric tests used due to normality violations; <sup>c</sup> Chi Squared Test, no significant difference.

## Procedural Checks

**Emotional memory task word encoding.** The precision of word categorization during initial word presentation was compared across groups to ensure that effects were not due to inability to process or encode words during initial presentation. Relationships were examined using Independent samples Kruskal-Wallis Test due to violations of normality that could not be corrected by transformations. Ability to encode words with correct categorizations was not significantly different across control participants (Mean= 31.00, SD=3.12), prodromal HD participants (Mean= 31.00, SD= 4.44), and manifest HD participants (Mean= 29.76, SD = 3.73), which was not significantly different across groups for pleasant ( $H(2) = 3.80$ , n.s.), unpleasant ( $H(2) = 1.43$ , n.s.) or neutral ( $H(2) = 1.24$ , n.s.) words. Additionally, valence ratings were not significantly different across groups (Table 5), suggesting that effects are not due to variations in the perception of emotional content or due to inability to recognize the stimuli as affective.

Table 5: Average participant rating of valence category demographics by group

Valence	Control (n=25)	Prodromal (n=26)	Manifest (n=27)	H (df)	Significance
Pleasant	1.94 (0.63)	1.93 (0.65)	2.16 (0.96)	0.034 (2)	0.98
Unpleasant	7.73 (0.67)	7.80 (0.72)	7.71 (0.81)	1.15 (2)	0.93
Neutral	5.07 (0.18)	5.03 (0.47)	4.91 (0.66)	0.15 (2)	0.56

*Note:* Valence rated on a 1 to 10 scale, with higher scores indicating more unpleasant ratings. One subject noted halfway through the task that they reversed the scale and this individual was excluded from this data. Significance based on an independent- Samples Kruskal-Wallis Test

**Control word list.** Regarding general semantic processing, all groups were additionally given a frequency based word memory task with a known effect (i.e., previous literature demonstrates better recognition of low frequency relative to high frequency words; May & Tryk, 1970, Rugg, Cox, Doyle, & Wells, 1995; MacLeod and Kamp, 1996; See Appendix E). Low frequency words were recognized better than high frequency words across control ( $Z=4.09$ ,  $p<$

0.001), prodromal HD ( $Z=2.77$ ,  $p < 0.01$ ), and manifest HD ( $Z=2.40$ ,  $p < 0.05$ ), using the Related-Samples Wilcoxon Signed Rank Test. Further, groups were not significantly different in regard to proportion recognition (i.e., high/low frequency recognition;  $H(2) = 0.62$ , n.s.).

**Control facial task.** In the control facial task (same/different discrimination), the control group correctly identified an average of 19.68 ( $SD=0.67$ ) faces, prodromal HD identified 19.12 ( $SD = 1.48$ ), and manifest HD correctly identified 18.69 ( $SD=1.71$ ) faces. There were significant differences between groups ( $H(2) = 6.44$ ,  $p < 0.05$ ) and post-hoc analyses suggested that differences were only between control and manifest HD patients ( $p < 0.05$ ), with no significant differences between prodromal and manifest HD or prodromal and control participants.

### **Hypothesis 1: Emotional Memory Compared Across Groups**

It was predicted that prodromal HD patients would demonstrate reduced emotional memory enhancement with HD patients failing to demonstrate an emotional memory effect. These hypotheses were partially supported, with altered emotional memory in manifest HD for recognition (Figure 2 and 3), though free recall was not significantly different within or between groups.

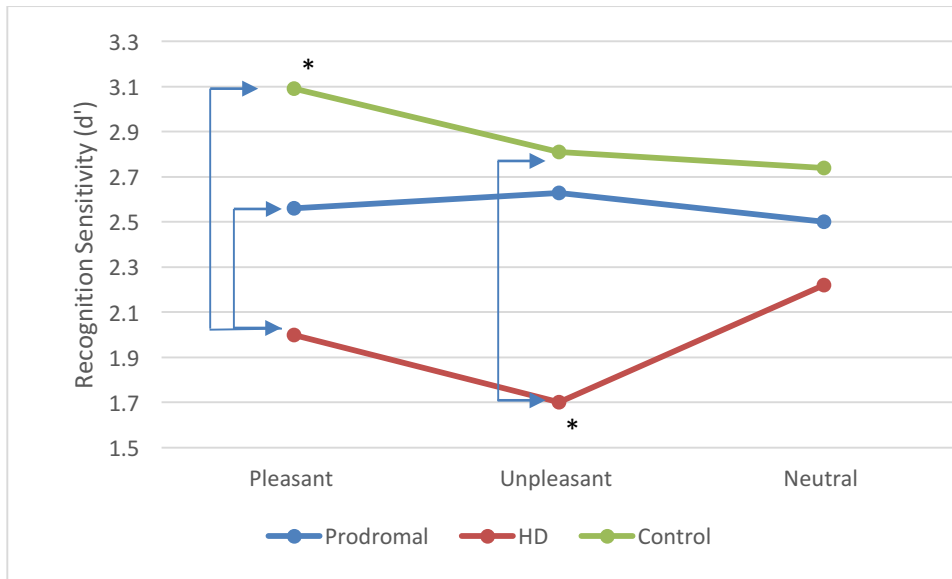
To examine within group differences, within group ANOVA repeated measures were used with planned comparisons (paired t-tests) examining emotional relative to neutral words recognition sensitivity (i.e.,  $d'$ ). In the control group, a trend was found for an overall effect ( $F(2,50) = 2.85$ ,  $p = 0.067$ ), with planned comparisons indicating pleasant word recognition was significantly higher than neutral word recognition,  $t(25) = 2.31$ ,  $p < 0.05$ , *Cohen's d* = 0.48, but unpleasant word recognition was not significantly different  $t(25) = 0.41$ , n.s. In prodromal HD, recognition was not significantly different across valence categories, ( $F(2,56) = 0.21$ , n.s.). In

manifest HD, recognition was significantly different across valence categories, ( $F(2,50) = 4.30, p < 0.05$ ), with planned comparisons indicating pleasant was not significantly different from neutral ( $t(28) = -1.30, n.s.$ ), but recognition of unpleasant words was significantly lower than recognition of neutral words,  $t(28) = -2.83, p < 0.01, Cohen's d = 0.46$ .

One-way ANOVA's were used across groups. For unpleasant d' only, the assumption of homogeneity of variances was violated, as assessed by Levene's test for equality of variances ( $p = 0.012$ ), but indicated equality of variances for pleasant and neutral recognition ( $p > 0.05$ ). Pleasant word recognition was significantly different between groups,  $F(2,78) = 11.17, p < 0.001, Cohen's d = 0.92$ . Post hoc comparisons using Tukey HSD test indicated significantly lower pleasant recognition in manifest HD patients (2.00, SD = 1.00) relative to controls (3.09, SD = 0.64;  $p < 0.001, Hedges g = 1.28$ ) and prodromal HD (2.56, SD = 0.86;  $p < 0.05$ ). Control and prodromal HD groups were not significantly different from one another. Neutral word recognition was not significantly different across control (2.74, SD = 0.78), prodromal HD (2.50, SD = 0.86), and manifest HD (2.22, SD = 1.00) groups,  $F(2,78) = 2.37, n.s.$  For unpleasant word recognition, there were statistically significant differences among groups using Welch's  $F(2, 49.625) = 17.193, p < 0.001$ , which is robust to violations of equality of variance. The test most appropriate for post hoc analysis of these results is the Games-Howell, which accounts for variance differences. This test revealed significant differences in unpleasant word recognition only between control (2.81, SD = 0.59) and manifest HD (1.70, SD=0.82,  $Hedges g = 1.54$ ), with prodromal not significantly different from either group (2.63, SD = 1.02).

Free recall group data was generally abnormal due to violations of normality, even though skewness and kurtosis was within acceptable limits (Table 2). As such, data was evaluated using non-parametric tests. Independent-Samples Kruskal-Wallis Test indicated

groups were not significantly different in free recall proportion of pleasant ( $H(2) = 2.264$ , n.s.), unpleasant ( $H(2) = 0.217$ , n.s.), or neutral words ( $H(2) = 5.63$ , n.s.). Subsequently, individual free recall variables were not examined in the remaining analyses.



**Figure 2.** Recognition sensitivity across valence for each group. Asterisks indicates significant difference from neutral within group, arrows indicate significant between group differences. Within the control group, pleasant word recognition was significantly higher than neutral word recognition and within manifest HD, unpleasant was significantly lower than neutral. Relative to controls, HD recognized significantly fewer unpleasant words, relative to both controls and prodromal HD, manifest HD recognized significantly less pleasant words.

The remaining hypotheses specifically examined differences in emotional memory across the HD group. Given that recall was not significantly different across groups, recall was not included in the remaining analyses. Five dependent variables were used throughout the remaining analyses when examining recognition sensitivity (i.e., pleasant  $d'$ , neutral  $d'$ , unpleasant  $d'$ , and emotional enhancement for pleasant (pleasant minus neutral) and unpleasant (unpleasant minus neutral)). As such, a Bonferroni correction for five variables was used with further analyses of

recognition, such that a significance level of  $p < 0.01$  was used, with  $p < 0.05$  considered a trend level relationship.

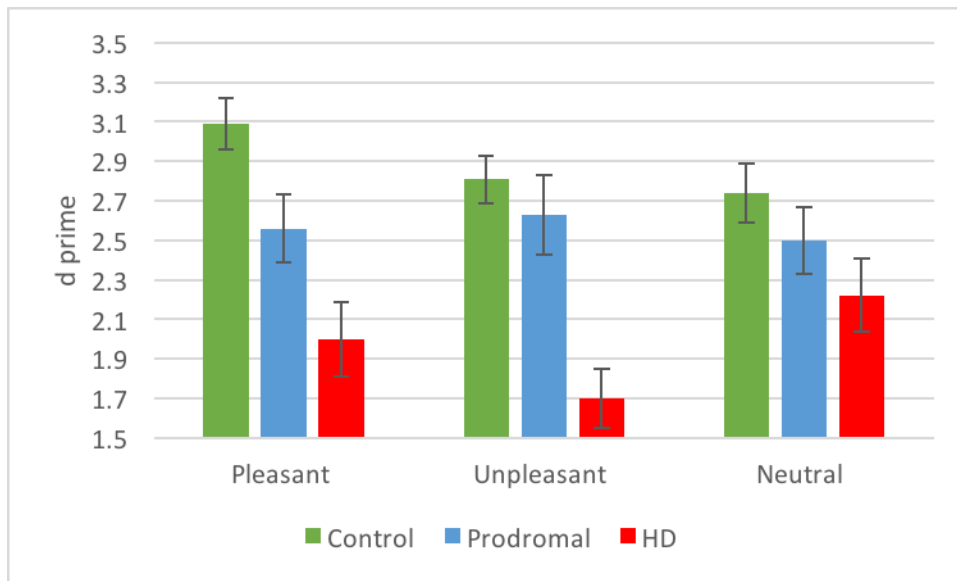


Figure 3. Recognition sensitivity across valence for each group with standard error. Error bars represent standard error. Within the control group, pleasant word recognition was significantly higher than neutral word recognition and within manifest HD, unpleasant was significantly lower than neutral. Relative to controls, HD recognized significantly fewer unpleasant words, relative to both controls and prodromal HD, manifest HD recognized significantly less pleasant words.

## Hypothesis 2: HD Progression and Emotional Memory

Burden of pathology was significantly related to decreased overall recognition discriminability of unpleasant words ( $r(49) = -0.48, p < 0.001$ ), with a trend negative relationship with decreased pleasant recognition sensitivity ( $r(49) = -0.30, p < 0.05$ ). Neutral word recognition was not significantly related. When comparing emotional enhancement (emotional minus neutral  $d'$ ), increased burden of pathology was related to decreased recognition of unpleasant words relative to neutral words in a trend relationship ( $r(49) = -0.33, p < 0.05$ ).

Months of progression (i.e., on a continuum of months until diagnosis to months with diagnosis) was significantly related to decreased overall recognition discriminability of pleasant words ( $r(53) = -0.43, p < 0.01$ ) and unpleasant words ( $r(53) = -0.51, p < 0.001$ ). Neutral word recognition was not significantly related. When comparing emotional enhancement, months of progression was significantly related at a trend-level to decreased unpleasant emotional enhancement ( $r(53) = -0.28, p < 0.05$ ).

Motor score was significantly related to decreased overall recognition discriminability of pleasant words ( $r_K(53) = -0.30, p < 0.01$ ) and unpleasant words ( $r_K(53) = -0.32, p < 0.01$ ). Neutral word recognition and emotional memory enhancement were unrelated to motor score.

Overall, recognition sensitivity for pleasant and unpleasant words was related to measures of HD pathology, and neutral word recognition was consistently unrelated. Trends were found to evidence emotional memory enhancement of unpleasant words relative to neutral when using disease burden and months of HD, but not motor score.

### **Hypothesis 3: HD Emotion Facial Recognition and Emotional Memory**

Spearman correlations indicated that total facial recognition was significantly related to  $d'$  for pleasant ( $r_s(53) = 0.42, p < 0.01$ ) and unpleasant words ( $r_s(53) = 0.39, p < 0.01$ ). These relationships were maintained when only examining performance on negative faces.

### **Hypothesis 4a: HD Executive Functioning and Emotional Memory**

Poorer executive function was related to decreased recognition discrimination for pleasant ( $r(51) = 0.53, p < 0.001$ ), unpleasant ( $r(51) = 0.56, p < 0.001$ ), and neutral words ( $r(51) = 0.36, p <$



0.01). Executive function was unrelated to difference scores of emotional words compared to neutral. Executive function was negatively associated with burden of pathology ( $r(47) = -0.38, p < 0.01$ ), months of disease ( $r(51) = -0.46, p < 0.01$ ), and motor score ( $r_k(51)=0.43, p < 0.001$ ), suggesting declining executive functioning with disease progression across measurements.

#### **Hypothesis 4b: HD Apathy and Emotional Memory**

In HD patients, apathy, as measured by AES-Total score, was not related to emotional word recall or recognition. Higher self-reported apathy demonstrated a trend relationship with decreased executive function composite score ( $r(51) = -0.29, p < 0.05$ ). Higher AES-Total (i.e., more apathy) was related to increased motor score ( $r_k(53) = 0.22, p < 0.05$ ), but was unrelated to burden of pathology ( $r(49)=0.15, n.s.$ ), and months of progression ( $r(53)= 0.25 = 0.069$ ).

#### **Additional Analyses**

Further analyses were conducted to examine the relationship of depression with emotional memory. Spearman correlations revealed that only pleasant recognition sensitivity demonstrated a trend relationship with depression as measured by total score on the PHQ-9 ( $r_s(53) = -0.28, p < 0.05$ ), with no other recognition variables related to depression.

Lastly, given multiple significant correlations between recognition sensitivity and other variables were found, two regression analysis were conducted to examine the unique variance these variables may be contributing to emotional memory recognition. Age was entered as a predictor given that age is found to be significantly related to emotional memory enhancement, such that older adults remember more positive information and less negative information

(Kensinger, 2008). The first regression analysis examined pleasant recognition sensitivity ( $d'$ ) as the dependant variable. Neutral recognition sensitivity (i.e., neutral  $d'$ ) was entered as a control variable with three predictors: age, executive function, and burden of pathology. Pleasant  $d'$  was significantly predicted by the variables in the regression model,  $F(4, 44) = 4.427, p < .0005.$ , Adjusted  $R^2 = 0.35$ . Neutral  $d'$ , age, and executive functioning significantly added to the prediction of pleasant  $d'$ , but burden of pathology was not a significant predictor (Table 6).

Table 6: Prediction of pleasant recognition sensitivity in HD patients

	B	SE B	$\beta$
Constant	2.72	0.58	
Neutral $d'$	0.30	0.12	0.31*
Age	-0.022	0.010	-0.26*
Burden of Pathology	-0.001	0.001	-0.061
Executive Function Composite	0.096	0.032	0.40**

\* $p < 0.05$ , \*\* $p < 0.01$ ; Note: B = Standardized regression coefficient;  $SE_B$  = Standardized error of the coefficient; Overall  $R^2 = 0.40$ ,  $\beta$  = Standardized coefficient; Adjusted  $R^2 = 0.35$ .

The second regression analysis examined unpleasant recognition sensitivity ( $d'$ ) as the dependant variable. Neutral recognition sensitivity (i.e., neutral  $d'$ ) was entered as a control variable with three predictors: age, executive function, and burden of pathology. Unpleasant  $d'$  was significantly predicted by the variables in the regression model,  $F(4, 44) = 8.87, p < 0.0005.$ , Adjusted  $R^2 = 0.40$ . Burden of pathology and executive functioning were significant predictors in the model, but age and neutral  $d'$  were not significant predictors (Table 7).

Table 7: Prediction of unpleasant recognition sensitivity in HD patients

	B	SE B	$\beta$
Constant	2.07	0.60	
Neutral d'	0.24	0.12	0.24
Age	0.019	0.011	-0.26
Burden of Pathology	-0.004	0.001	-0.38**
Executive Function Composite	0.075	0.033	0.27*

\* $p < 0.05$ , \*\* $p < 0.01$ ; Note: B = Standardized regression coefficient;  $SE_B$  = Standardized error of the coefficient; Overall  $R^2 = 0.45$ ,  $\beta$  = Standardized coefficient; Adjusted  $R^2 = 0.40$ .

## DISCUSSION

This study sought to examine emotional memory for words of pleasant, unpleasant, and neutral valence, equated on arousal, in prodromal and manifest HD patients relative to control participants. The study further investigated factors that relate to emotional memory, including those hypothesized to share underlying neurocircuitry (apathy and emotional facial recognition) and those that may contribute to reduced emotional memory effects (executive functioning and HD disease progression).

It was predicted that emotional memory enhancement for pleasant and unpleasant words would be significantly reduced for prodromal HD patients relative to control participants and absent in manifest HD patients relative to control participants. This hypothesis was partially supported. Rather than the expected reduced emotional memory enhancement, prodromal HD patients failed to demonstrate an emotional memory enhancement for pleasant words, as was found in the control group. The manifest HD group also failed to demonstrate an emotional memory enhancement, which was further evidence by significantly lower pleasant recognition compared to controls, despite no significant difference between manifest HD and control participants on neutral recognition sensitivity. Across groups, neutral word recognition ( $d'$ ) and overall encoding rates (i.e., words categorized during the encoding trial and not missed) were not significantly different, suggesting that effects are not due to overall recognition performance or ability to encode information in the time allotted. Unexpectedly, for unpleasant words, manifest HD patients not only had reduced performance relative to controls, but also demonstrated

significantly lower recognition performance relative to their own performance on neutral word recognition, possibly evidencing a decrement for negative words.

Reduced emotional memory effects are consistent with studies using other disease populations with frontal dysfunction (FTD; Kumfor et al., 2013; St. Jacques et al., 2014), frontal and mild amygdala involvement (ALS; Sedda, 2014), and subcortical neurodegeneration impacting dopaminergic networks (PD; Hälbig et al., 2011). Further, while more difficulty with negative recognition in manifest HD was unexpected, HD patients did show the expected effect of reduced emotional memory for pleasant and unpleasant words, while PreHD patients did not evidence significantly lower recognition rates relative to controls. One explanation may be that cognitive processes at encoding caused HD patients to either not fully encode the stimuli, such as suppressing their emotional response to the stimuli due to poor emotional regulation abilities. While this is speculative, studies using suppression have demonstrated reduced memory for emotional stimuli (Gross & John, 2003; J. P. Hayes et al., 2010). In regard to lower recognition for specifically negative words, difficulty processing negative information is consistent with some findings in Parkinson's disease (Hälbig et al., 2011; Wieser et al., 2006), and in HD studies which find more difficulty recognizing negative compared to positive emotional faces and prosody (Speedie, Brake, Folstein, Bowers, & Heilman, 1990; Croft, McKernan, Gray, Churchyard, & Georgiou-Karistianis, 2014).

Several additional factors may have contributed to poorer recognition of negative affective words. In recognition tasks that require participants to respond in a dichotomous manner (i.e., yes or no), effects of “remembering” and “knowing” are conflated (Kalenzaga, Piolino, & Clarys, 2004). It has also been suggested that emotional information feels more familiar by nature, therefore increasing the likelihood of endorsing “remembering” an emotional

item (Sharot, Delgado, & Phelps, 2004). This interpretation would suggest a bias towards negative information feeling more familiar rather than an impairment in recognition. It is important to note that no differences were found between groups in proportion of emotional items freely recalled, suggesting this may be unique to recognition and account for the observed differences. Interestingly, this is consistent with a study examining emotional memory after administration of a dopamine antagonist (i.e., blocks dopamine), in which free recall remained unaffected, but the antagonist reduced recognition with notable increases in false positive responses (Gibbs, Naudts, Spencer, & David, 2010). Additionally, it has been suggested that negative word recognition, by nature, is more difficult than positive word recognition simply due to semantic cohesiveness that causes more false errors (Maratos, Allen, & Rugg, 2000; Kalenzaga, Piolino, & Clarys, 2004). While semantic cohesiveness was controlled for across word lists and word banks, it is possible that the nature of negative words may be qualitatively different when placed among other negative words, which may have impacted results. Lastly, studies specifically examining response bias suggest that bias alone, and not accuracy, may account for differences in emotional memory recognition data (Dougall & Rotello, 2007), including the positivity bias previously discovered in older adults (Kapucu, Rotello, Ready, & Seidl, 2008). This may account for differences in memory for pleasant and unpleasant stimuli. Future research is needed to characterize bias in HD and the mechanisms that contribute to any bias that may account for the significant decrease in unpleasant recognition sensitivity.

Of note, in the control group, memory for unpleasant words was not significantly higher than neutral words, which may be due to the nature of negative words, as outlined above. Failure to elicit higher recognition of unpleasant stimuli in a control group has been reported in other studies using recognition measures (Kalenzaga, Piolino, & Clarys, 2004; Hälbig et al., 2011),

especially when controlling for arousal, which is reported to be a large contributor to increased negative recognition (Hermans et al., 2014; Kensinger & Corkin, 2004; Lewis et al., 2007; Sharot et al., 2007). However, control participants did demonstrate emotional memory enhancement of pleasant words relative to neutral words and this relationship was absent in prodromal and manifest HD patients.

### **HD Emotional Memory and Disease Progression**

It was predicted that as HD progresses, emotional memory would decrease. This hypothesis was generally supported. Across multiple measures of disease progression, further progression was related to decreased pleasant and unpleasant recognition sensitivity, but was consistently unrelated to neutral recognition. Trends were also observed between decreased emotional memory enhancement of unpleasant relative to neutral words, for both months of HD and burden of pathology. Additionally, being able to examine disease status as a continuous measure allowed for quantification of disease status, as some studies have suggested qualitative differences in early disease compared to later disease (Kalenzaga, Piolino, & Clarys, 2004). This is consistent with other disease models, such as FTD and PD, which similarly are hypothesized to experience emotional processing deficits as the diseases progress (Kumfor et al., 2013; Hälbig et al., 2011).

Given that HD is a multi-faceted disease, the relationship with progression could occur for many reasons, including network breakdown, regional atrophy, altered dopaminergic pathways, or any combination of these factors. As previously described, as HD progresses, specific volume loss in the striatum, insula, ACC, PFC, and the amygdala occur (Dogan et al.,

2015; Nopoulos et al., 2010; Mason et al., 2015), areas which have also been implicated in affective appraisal and emotional memory enhancement (Cunningham, Zelazo, Packer, & Van Bavel, 2007).

Beyond specific areas that demonstrate atrophy, the breakdown of neural networks as the disease progresses may be related to functional and cognitive changes across the disease (Dumas et al., 2013; Dogan et al., 2015). Neural network breakdown has been found as HD progresses (Dumas et al., 2013) and has been related to observed cognitive changes in HD (Misiura et al., 2017). Through examination of networks activated during cognitive tasks and during the resting state, Dogan et al. (2015) suggested that while subtle changes in HD may not be apparent when examining atrophy in specific regions, altered functional connectivity is detectable in prodromal HD and becomes more widespread as the disease progresses. They suggest that prodromal patients evidence a more “cognitive network” (rather than “motor network”) dysfunction, which includes the caudate, putamen, insula, lateral PFC, premotor/supplementary motor areas, and parietal cortex and is related to working memory and reasoning task performance. They further note the DLPFC is a primary area susceptible to network disruption in the prodromal stage. As the disease manifests, they note the “cognitive network” dysfunction increases and further expands to include the mPFC. Similarly, in a study examining individuals with moderate and severe TBI, Rosenberg et al. (2015) found that injury severity uniquely predicted emotional facial recognition performance, which may be related to disruption of white matter tracts.

Further, as HD progresses, the disease is also notable for changes in dopaminergic pathways, though the exact alterations across the disease remain unclear (Schwab, Garas, Drouin-Ouellet, Mason, Stott, & Barker, 2015). Regardless, several studies implicate dopaminergic involvement in emotional processing in healthy individuals, through localized



receptors in the mPFC (Lauzon, Bishop, & Laviolette, 2009), the mesolimbic dopaminergic network (Alvarsson, Caudal, Björklund, & Svenningsson, 2016; Gibbs, Naudts, Spencer, & David, 2010), and downstream effects that influence norepinephrine (Tully & Bolshakov, 2010). However, the exact mechanisms of influence on emotional memory are unknown (Gibbs, Naudts, Spencer, & David, 2010). Using neutral and negative words, an administered dopamine ligand was demonstrated to show increased binding in response to negative emotional words in the left hemisphere, specifically in the amygdala, mPFC, and inferior frontal gyrus (Badgaiyan, Fischman, & Alpert, 2009). When administered a dopamine antagonist (i.e., sulpiride or similar), participant's evidenced decreased emotional memory, specifically for recognition but not free recall (Mehta, Hinton, Montgomery, Bantick, & Grasby, 2005; Gibbs et al., 2010), consistent with the present results. Additionally, in a subsequent study, Badgaiyan (2010) examined striatum activity during negative affect and observed dopamine binding in the dorsal striatum (i.e., caudate and putamen), which is known to be impacted in HD. The author suggests that while positive emotions are processed through the ventral striatum (i.e., the "reward system" which includes the nucleus accumbens), negative emotions are processed through the dorsal striatum. Lastly, in PD patients, deep brain stimulation of the subthalamic nucleus was observed to improve immediate emotional memory for negative arousing stories relative to neutral stories, purportedly through the dopaminergic system (Schneider et al., 2003). Conversely, dopamine has also been suggested to reduce emotional memory, with better recall and recognition of negative images when PD patients are off medication (i.e., dopamine depleted; Hälbig et al., 2008, 2010). This suggests that alterations in the dopaminergic network impact emotional memory, although the exact mechanisms are unknown.

Given the heterogeneity of HD, it is important to note that findings were relatively consistent across all three measurements of HD progression. While motor score is measurable and was generally obtained concurrently with the emotional memory task, low scores do not account for medication effects that may reduce motor symptoms or the variance within prodromal HD patients who have no motor signs (i.e., those far from manifestation and close to manifestation are both quantitatively the same). Burden of pathology, however, allows for estimation using known variables (i.e., age and CAG repeats), but is limited by the need for a quite expensive genetic test to determine CAG repeats. Further, it does not account for variability in age of onset, such that one individual may be manifest and the other prodromal, yet both have the same burden of pathology. Instead, burden of pathology is conceptualized as a measure of life-time disease exposure (Dogen et al., 2013; Penny et al., 1997). The third measurement, months of HD, was used to estimate time *until* onset and time *since* onset, which allowed for the inclusion of more patients (i.e., those manifested without known CAG repeats) and took disease status (prodromal or manifest) into consideration. However, this measurement relies on retrospective estimation of disease onset in manifested patients who did not have date of onset documented in their medical record, adding variability to the data. Given that all measures of progression have weaknesses, multiple methods of measurement were used in the current study to examine disease progression. The results across measurements produced a consistent pattern, suggesting that a relationship between emotional memory and HD progression remains despite the differences in methodology.

## **Emotional Memory and Emotional Facial Recognition**

Emotional face recognition deficits are consistently reported for manifest HD (Bora, Velakoulis, & Walterfang, 2016) and are one of the few deficiencies evident in prodromal HD (Johnson et al., 2007). Given emotional face recognition includes appraisal of emotion, it was predicted to be related to emotional memory enhancement due to shared underlying mechanisms. This hypothesis was partially supported. Better performance on emotional face recognition was related to increased emotional word recognition sensitivity for both pleasant and unpleasant words in prodromal and manifest HD patients. This relationship was restricted to emotional words, such that there was not a significant relationship between emotional face recognition and neutral word recognition sensitivity.

Overall, emotional face recognition has had inconsistent results across the literature. In a study by Dogan et al. (2013), the authors suggest that impairment in HD starts as relatively heterogeneous, then moves into more homogeneous impairments as the disease progresses. They further note that networks include cortical and subcortical networks with specific impairment in the striatal-thalamo-cortical loop. In one study using Parkinson's patients, participants in the early stages of PD displayed difficulty identifying negative emotional faces, and as the disease progressed, this impairment extended to positive emotional faces as well (Lin, Tien, Huang, Tsai, & Hsu, 2016). This is a similar pattern of impairment outlined in a review by Bora, Velakoulis, and Walterfang (2016), who noted studies have found impairments in negative emotional facial recognition in prodromal HD, which extended into positive emotion identification as the disease progressed. They also found that performance was consistently related to disease progression, basic facial recognition ability, and verbal fluency. Similarly, manifest HD patients have been found to evidence poorer recognition for negative emotions, even when difficulty was controlled

for (Snowden et al., 2008). Contrary to these results, a study of PD patients using deep brain stimulation of the subthalamic nucleus, found stimulation did not to improve emotional facial discrimination, which the authors suggest indicate a stronger cognitive component inherent in the task (Schneider et al., 2003).

Despite overlapping neurocircuitry, there are distinct differences in the ability to distinguish emotional facial expressions and emotional memory as examined in this study. First, one can argue that emotional facial recognition is also arousing, while the words in this study were specifically chosen to be equated on arousal. Arousal, often primarily associated with the amygdala (Hermans et al., 2014; Kensinger & Corkin, 2004; Lewis et al., 2007; Sharot et al., 2007), may be influenced by amygdala atrophy present in HD (Mason et al., 2015). Second, visual processing is required for facial recognition, but the current study relied more on semantic networks. Within this study, manifest HD patients performed significantly worse on a very basic task of facial discrimination. Prior research suggests that when examining performance in prodromal HD, performance on an emotional facial recognition task is directly related to visual processing regions rather than limbic regions (Jacobs, Shuren, & Heilman, 1995; Bora et al., 2016). Overall, these results suggest that the two constructs have some shared mechanisms, but the current study may best represent the processing of valenced stimuli, independent of arousal or visual processing deficits.

### **Emotional Memory and Apathy**

It was predicted that increased apathy would be related to decreased emotional memory, which was not supported. Apathy did not relate to emotional memory of pleasant or unpleasant words or enhancement (neutral relative to affective words). Previous studies have suggested that

apathy is distinct from depression and may be a result of frontal dysfunction inherent in HD (Naarding, Janzing, Eling, van der Werf, & Kremer, 2009). In a study examining psychiatric difficulties broadly (including apathy, among others), no relationship was found with regional volume changes in prodromal HD (Misiura et al., 2017). However, others have suggested apathy is the only psychiatric symptom in HD that is consistently found to be related to disease progression (Van Duijn, Kingma, & Van der Mast, 2007), suggesting underlying neural changes in HD associated with increased apathy.

While the inability to identify an effect may be due to the relatively small sample size, it is also possible that apathy symptoms across the disease progression are not represented linearly. While this study used prodromal and manifest HD patients, studies examining apathy in HD often study these groups independently. In one such study examining prodromal HD patients using the FrSBe (which includes an apathy scale), the relationship with self-reported frontal behaviors was found to be an inverted “U” shape (Duff et al., 2010), such that those furthest away from diagnosis and those closest to diagnosis evidenced the lowest reported symptoms relative to those in the mid-point, which evidenced the most. The authors suggest that this may indicate decreased awareness as patients near manifestation. In manifest HD, patients were found to agree with an informant in the early stages of the disease in self-reported frontal behavioral symptoms, but become more discrepant as the disease progresses (Hergert, Sanchez-Ramos, Cimino, 2015). This disparity across the span of the disease may confound any relationship with apathy and emotional memory. Lastly, the lack of relationship may also suggest that shared neural involvement (e.g., mPFC; Duff et al., 2010; Van Duijn, Kingma, & Van der Mast, 2007) may only be one aspect of the emotional memory process and therefore fail to demonstrate a relationship.

## **HD Emotional Memory and Executive Functioning**

It was predicted that executive functioning would be positively correlated to emotional memory and emotional memory enhancement, which was partially supported. In HD patients, better executive function related to increased recognition sensitivity for all valence categories, not just emotional words. However, there were no significant relationships to difference scores of affective relative to neutral words, suggesting that better executive functioning increases recognition overall, without any specific valence effect in HD. This is not entirely unexpected as overall recognition accuracy and recognition processes have been demonstrated to be influenced by executive processes, particularly through recruitment of the posterior cingulate cortex (Kumfor et al., 2013).

Regression analyses were used to determine the ability of executive functioning to predict performance when controlling for general recognition ability (i.e., recognition of neutral words), disease progression, and age. Executive functioning remained a unique predictor of emotional word recognition sensitivity for both pleasant and unpleasant words, suggesting influence beyond general ability to perform the recognition task. It is not surprising that executive functioning would still predict beyond disease progression given that while executive dysfunction is considered common in HD, degree of impairment in executive functioning is not directly related to disease progression, per se (Dumas et al., 2013).

Executive functioning is proposed to vary in importance from influencing emotional memory (Pessoa, 2009) to being the primary causative factor for reduced emotional memory in disease models (Borg et al., 2011; Broster et al., 2012), occurring through controlled or elaborative processes in the PFC (Kensinger & Corkin, 2004; Ritchey, LaBar, & Cabeza, 2011; Talmi, 2013). Further, diseases with primary executive dysfunction, such as FTD, are found to

have reduced emotional memory despite intact amygdala (Kumfor et al., 2013). Taken together, these results suggest a unique influence of executive functioning on the recognition of emotional words, consistent with the theory proposed by Broster et al. (2012) based on Borg et al. (2011).

### **Valence Effects in HD Patients**

Within manifest HD patients, results suggest a loss of emotional memory enhancement for pleasant words and a reduction, or specific impairment, in the memory of unpleasant words. Given relationships were found for each valence with multiple variables, the ability to predict pleasant and unpleasant words was examined. As noted above, executive functioning was a positive predictor for both pleasant and unpleasant words, such that better executive functioning predicted better recognition.

Regarding pleasant word recognition, neutral word recognition (i.e., general discrimination ability) was a positive predictor while age was a negative predictor. This is contrary to the expected age-related positivity effect, which has found that older adults demonstrate increased memory for pleasant unarousing words while younger adults evidence enhancement for both pleasant and unpleasant valence (Kensinger, 2008), and this effect increases as individuals age (see Reed, Chan, Mikels, 2014 for review). In HD patients, chance of manifestation or chance of death due to HD increases with age. While burden of pathology was not a significant predictor, age may be related to disease progression rather than normal aging. Given that age and neutral recognition were control variables, this suggests executive dysfunction is the primary determinant of recognition for pleasant words in HD. This is consistent with the proposal that executive function will determine emotional memory enhancement in neurodegenerative disease models (Broster et al., 2012; Borg et al., 2011) and

supports the relative importance of frontal functioning in emotional memory (Kensinger & Corkin, 2004; Dolcos et al., 2012).

For unpleasant words, burden of pathology was a unique predictor, such that higher burden of pathology was related to decreased recognition sensitivity when controlling for neutral recognition and executive functioning. This further suggests that as the disease progresses, negative recognition is selectively reduced by disease related factors, in addition to executive dysfunction, and not simply due to reduced ability to discriminate in a recognition task. Interestingly, in PD patients, a “negativity bias” has been proposed to occur in the absence of dopaminergic medication, with patients evidencing decreased negative emotional memory on dopaminergic medication, but normal memory for unpleasant stimuli when off medication (Hälbig et al., 2011). Multiple studies suggest more difficulty with negative emotional facial recognition in PD (Lin et al., 2016), which has also been found in HD (Snowden et al., 2008; Baez et al, 2015) and Bora et al. (2016) suggest this may be related to dysfunction of the striatal-thalamocortical circuits. Badgaiyan (2010) has also proposed that negative emotions are processed through the dorsal striatum (i.e., caudate and putamen), which are the most prominent areas of dysfunction in HD.

More broadly, a differentiation of pleasant and unpleasant recognition abilities suggests valence specific effects in HD. Specific valence predictions were not made in this study as there are disagreements on the neural basis of pleasant and unpleasant stimuli processing. Theories have considered valence as a unipolar construct (“Bipolar”; Wundt, 1897/1998), two parallel processes (“bivalent”; e.g., Watson & Tellegen, 1985; Cacioppo, Gardner, & Berntson, 1997), and more recently, a dynamic and fluid “affective workspace” that responds to valence regardless of positivity or negativity (Barrett & Bliss-Moreau, 2009; Lindquist, Satpute, Wager,



Weber, & Barrett, 2016; Man, Nohlen, Melo, & Cunningham, 2017). However, there is currently no single, agreed upon model of valence processing that can account for all findings in the literature (Man et al., 2017; Barrett & Bliss-Moreau, 2009). In a large neuro-imaging meta-analysis, Lindquist, Satpute, Wager, Weber, and Barrett (2016) evaluated the support for each model of valence within neuroimaging studies and concluded the “affective workspace” model fit best, which they further relate to the salience network. While few valence specific effects were found, they noted a relative increase in activation of the amygdala and insula in response to negative material (despite activation present generally for all conditions) and relative increased activation in the mPFC and ACC in response to positive material. When using fMRI neuroimaging during categorization of pleasant and unpleasant words, Maddock, Garrett, and Buonocore, (2003) controlled for all possible non-emotional variables (e.g., imagery, frequency, part of speech, etc.). While some brain regions demonstrated activation during both pleasant and unpleasant word categorization (i.e., posterior and subgenual cingulate cortex and anteromedial orbital prefrontal cortex), differences emerged as well. They found increased activation in the right frontal pole when viewing pleasant words but not unpleasant, and increased activation in the right amygdala for unpleasant but not with pleasant. While this study did not adequately control for arousal, other studies have suggested involvement of the amygdala despite low levels of arousal (Garcia-Garcia, Kube, Gaebler, Horstmann, Villringer, & Neumann, 2016). Taken together, this may indicate that even in the absence of arousal (or with arousal controlled), amygdala function in HD may contribute to decreased memory of negative emotional words with more prefrontal involvement contributing to the loss of emotional enhancement for pleasant emotional words.

## **Limitations and Future Directions**

The primary limitation of this study is the relatively small sample size, which may have reduced the ability to detect more subtle relationships with emotional memory enhancement (i.e., affective minus neutral recognition) or free recall. While large cohort studies, such as Predict-HD, have detected deficits in emotional facial recognition prior to motor symptom onset (Johnson et al., 2007), other emotional processing deficits have not been examined in these large-scale studies. Future large-scale studies should incorporate other measures of emotional processing, such as emotional word or story memory, which are not influenced by possible visual processing deficits, but rather rely on relatively preserved language abilities. This may also allow for correlation of results to neuroimaging data, possibly disentangling the impact of amygdala atrophy and frontal functioning on emotional processing deficits. Given that emotional facial recognition tasks are inherently visually mediated and facial stimuli are naturally unbalanced (i.e., over representation of negative emotions and differences in difficulty across stimuli), future research may wish to include emotional memory as a marker for disease status and separate emotional processing from executive dysfunction.

Additionally, the nature of the emotional memory task limited who could be included in the study. Patients were required to be relatively independent and cognitively capable of completing the task, which often requires patients to be early in the disease process and may have selected for individuals with less impairment in executive functioning, even in the more progressed patients. Therefore, it is unknown the extent to which these deficits in emotional memory continue as the disease progresses. This is further complicated by the measurement of HD progression, which requires subjectivity and estimation. Future research, especially in the context of a larger

study, would benefit from more accurate disease progression measurements (e.g., striatal atrophy) or from following patients over time.

Further, due to the extreme high rates of psychopathology in HD (Paulsen, Ready, et al., 2001; Shiwach, 1994), it is near impossible to exclude those receiving treatment for or diagnosed with a psychological disorder, which may impact results. Inclusion of a “psychiatric group” to control for the effects of psychotropics on emotional memory may be beneficial in future studies. Regarding prodromal HD patients, these individuals are self-selected to participate in research and do not yet require regular office visits for motor symptom management. As such, prodromal HD patients are often seeking psychiatric treatment prior to manifestation, which may limit generalizability and possibly contributed to the failure to find a relationship with apathy symptoms. Due to difficulties with awareness, measurements of actual psychopathology may vary across the disease and may become inaccurate if insight is not intact, which may occur before manifestation (Duff et al., 2010) or after motor symptom onset (Hergert, Sanchez-Ramos, Cimino, 2015). If changes in insight are present, depression may be inaccurately reported, influencing results. However, increased depression is often found to be related to increased memory for unpleasant stimuli (Hamilton & Gotlib, 2008) and is likely not contributing to the present results. Regarding medications for motor symptoms, these also varied in the type of medication prescribed. While only nine patients were using medication to treat chorea, studies in PD patients have suggested that dopamine may impact emotional memory processing (Hälbig et al., 2008, 2010) and dopaminergic changes in HD are still poorly understood (Schwab et al., 2015).

Beyond patient characteristics, methodology may also be a limiting factor. Participants were asked to categorize words during encoding, utilizing an explicit encoding task, resulting in bottom-up processing (Garcia-Garcia, Kube, Gaebler, Horstmann, Villringer, & Neumann, 2016),

which may have produced different results than an implicit encoding task and increased the likelihood of remembering emotional words (Ferré, Fraga, Comesaña, & Sánchez-Casas, 2016). Future research should examine if the relationship with executive functioning remains when incidental learning is used or when learning occurs within a context (e.g., emotional stories). There were also limitations with the stimuli used. The control group did not demonstrate emotional enhancement of unpleasant words. While other studies have had similar effects using a recognition task in controls with differences found in the disease patients (Kalenzaga, Piolino, & Clarys, 2014; Hälbig et al., 2011), it may suggest that a decline in memory for unpleasant words may be due to a third variable problem rather than a reduction in emotional memory for negative information. Further, while many aspects were controlled within the study, it is near impossible to control for all word characteristics. For example, this study did not control for distinctiveness or imaginability, which are two aspects that may impact emotional memory of verbal stimuli (Watts, 2015). Replication of the current results is needed to ensure that effects are not related to stimulus characteristics.

Furthermore, though arousal level of the stimuli was statistically controlled for, patients were not required to rate words on arousal. In manifest HD, patients have previously been found to overestimate the intensity of emotional pictures (de Tommaso et al., 2013), suggesting differences in arousal perception as the disease progresses. While it is difficult to disentangle arousal and valence effects, arousal is proposed to be more related to amygdala activation (Hermans et al., 2014; Kensinger & Corkin, 2004; Lewis et al., 2007; Sharot et al., 2007), which is known to be impaired in HD (Mason et al., 2015). Further, even in the prodromal stage of the disease, reduced functional connectivity of the amygdala has been found (Mason et al., 2015).

Taken together, although valence effects have been uncovered, future studies should examine the impact of arousal on emotional memory and explore the interaction of valence and arousal in HD.

Although a difference was suggested between pleasant and unpleasant word recognition in HD, the mechanism contributing to this difference is unknown. One explanation may be the breakdown occurring during the evaluative process, but this must be further examined. Within the “integrative reprocessing model” proposed by Cunningham, Zelazo, Packer, & Van Bavel, (2007), evaluation of a stimuli is noted to occur with several iterations, with determination of pleasantness or unpleasantness as part of either initial evaluations (i.e., for overlearned or automatic evaluations) or in subsequent evaluations (e.g., for ambiguous evaluations or when relationship to other networks are required, such as incorporating goals). They further propose a neuroanatomical model which includes direct processing from the thalamus to both the amygdala and prefrontal cortex. Subsequent processing then occurs through the ACC, OFC, hypothalamus and insula. As such, it is unknown if the dysfunction in HD occurs during appraisal as part of this system, which stage of appraisal, or if dysfunction occurs during retrieval on recognition tasks. Future studies should explore these mechanisms. Additionally, in a related body of literature, increased executive dysfunction and lack of sensitivity to punishment in manifest HD have been found to be associated (Johnson, Potts, Sanchez-Ramos, & Cimino, 2016), with dysfunction present in the evaluation of reward and punishment in patients nearing HD onset (within 5 years; Enzi et al., 2012). Though reward and punishment also involve many different mechanism, they also have shared neural circuitry as well. Future studies should examine the extent to which shared appraisal dysfunction occurs in reward/punishment processing and emotional stimuli processing, and if more difficulty with negative emotional recognition is related to reduced punishment sensitivity.

## **Conclusion**

The present study was the first to examine emotional word memory in prodromal and manifest Huntington's disease (HD) patients. While control participants demonstrated better recognition for pleasant words, both prodromal HD and manifest HD patients failed to evidence emotional memory enhancement. Compared to control participants, manifest HD patients evidenced reduced recognition for only emotional words with no differences between groups for recognition of neutral words. Additionally, manifest HD patients demonstrated significantly lower recognition sensitivity of negative relative to neutral words, suggesting selective difficulty with negative stimuli. Across the prodromal and manifest HD patients, emotional word recognition was related to disease progression, executive functioning, and emotional facial recognition. While executive dysfunction predicted both pleasant and unpleasant recognition, disease progression uniquely predicted unpleasant recognition. Given past findings of emotional processing and known pathology in HD, this may indicate that amygdala dysfunction in HD contributes to decreased memory of negative emotional words while prefrontal activation contributes to the loss of emotional enhancement for pleasant emotional words. These results have implications for monitoring disease progression and contribute to the understanding of the vast amount of emotional dysfunction present in HD.

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## APPENDIX A: DETERMINING CAPACITY TO CONSENT IN HD

While it is unlikely many patients will need specific procedures to determine capacity because of the need to remain independent to be enrolled in this study, it is possible some participants may need special procedures due to the prevalence of cognitive impairment in HD. As such, steps outlined below will detail the special procedures that will be taken to ensure that the participant has the capacity to consent and properly understands the study procedures. The main tenants of consent involved the assessment of: understanding, appreciation, reasoning, and expressing a choice (Appelbaum & Grisso, 1988).

- 1) If a participant has a recent (within 4 months) score on the MoCA of 22 (within four months) or above or a MMSE above 25, then it is determined that the individual has capacity for consent. The MOCA cut-off is based on a study in Parkinson's disease by Karlawish et al. (2013), in which they suggests that at a score of 22 or above had a sensitivity of 94% when identifying those with difficulty understanding, appreciation, reasoning, and expressing a choice, assessed through a standard capacity assessment measure.
- 2) If an individual does not have recent enough MoCA, the test will be administered prior to consent (if feasible) or the appropriate research questions will be asked to determine in the individual is able to understand the purpose of the study.
- 3) If an individual scores lower than a 22 on the MOCA, the patient will be asked a series of questions to ensure their understanding of the study. Past research indicates that asking questions about the procedures and assessing understanding from the participant is an adequate way to measure capacity to consent (Berghmans, 2001). If the individual does not answer the questions correctly, he or she will be excluded from the study. The studies posed to the individual will be:
  - a. Are we offering you your usual medical care, or are we asking you to be in a research study?
  - b. Must you take part in this study, or is it OK to say 'no'?
  - c. Tell me the main things that you would do in this study
  - d. Tell me the main risks of this study
  - e. Tell me the benefits of this study
  - f. Will this study mainly help you or others?
  - g. Considering the risks and benefits we have discussed, would you like to take part in this study?
  - h. Why?

Policy and Procedures for Assessing Capacity To Consent for Research available through UC Davis Alzheimer's Disease Center will be used. Specific guidelines dictate how responses meet or fail to meet the four main aspects of consent: understanding, appreciation, reasoning, and expressing a choice.

## APPENDIX B: USF IRB APPROVAL FOR HUMAN RESEARCH



RESEARCH INTEGRITY AND COMPLIANCE  
Institutional Review Boards, FWA No. 00001669  
12901 Bruce B. Downs Blvd., MDC035 • Tampa, FL 33612-4795  
(813) 974-5638 • FAX(813)974-7091

January 28, 2016

Patricia Johnson, M.A.  
Psychology  
4202 E. Fowler Avenue  
PD3121  
Tampa, FL 33620

RE: **Expedited Approval for Initial Review**  
IRB#: Pro00022502  
Title: Word processing and emotion in Huntington's disease (HD)

**Study Approval Period: 1/28/2016 to 1/28/2017**

Dear Dr. Johnson:

On 1/28/2016, 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):**

[Study Protocol \(Version 1: 12/11/15\)](#)

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

[Consent Form Control \(Version1: 1/26/16\).pdf](#)

[Consent Form HD/PreHD \(Version 1: 1/26/16\).pdf](#)

\*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).

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

## APPENDIX C: VALENCE CATEGORIZATION ENCODING DIRECTIONS

You will see a list of words one at a time and be asked to rate if you feel the word is: Pleasant (P) Neutral (N) or Unpleasant (U)

A Pleasant word is something that may make you feel happy, pleased, satisfied, content, or hopeful. An Unpleasant word is something that may make you feel unhappy, annoyed, unsatisfied, gloomy, despaired, or scared. A Neutral word is neither pleasant or unpleasant to you.

The computer will go on to the next word automatically, not just after you answer. You will only have a few seconds before the computer goes on to the next word. Here are a few for practice.

kindness: Is this word Pleasant, Neutral, or Unpleasant?

(feedback given) kindness is often seen as a pleasant word because it makes people feel happy, pleased, satisfied, content, or hopeful. For this word "P" is selected.

kill: Is this word Pleasant, Neutral, or Unpleasant?

(feedback given) kill is often seen as a unpleasant word because it makes people feel unhappy, annoyed, unsatisfied, gloomy, despaired, or scared. For this word "U" is selected.

door: Is this word Pleasant, Neutral, or Unpleasant?

(feedback given) door is often seen a neutral words since it is not really pleasant or unpleasant. For this word "N" is selected

Remember these ratings are your own opinion of the word. If a word has more than one meaning, answer based on the first meaning you think of. Try not to over think your answer - go with your initial reaction.

Now we will begin. Look at each word and rate it as Pleasant, Neutral, or Unpleasant. Please rate it as quickly but as accurately as you can.

## APPENDIX D: PILOTING PROCEDURES AND RESULTS

Piloting was conducted using several different procedures before arriving at the current methodology, which was used to establish the time exposure for controls to avoid ceiling effects. A new set of words needed to be created due to difficulty controlling for arousal, frequency, and semantic relatedness using current word sets. Word lists were partially derived from the unarousing words used in Kensinger et al. (2008), but required new neutral words to equate on arousal. The following data was collected with the same methodology of the current study in regard to the emotional memory task. However, the executive function measures were not administered and therefore the control was approximately 10 minutes after the main task rather than approximately 30 minutes later.

The following words were the pool of words in which the lists were made from.

<b>Word Bank By Valence</b>		
<b>Positive</b>	<b>Neutral</b>	<b>Negative</b>
<b>useful</b>	utensil	<b>blister</b>
<b>reward</b>	appliance	<b>bored</b>
<b>cozy</b>	pamphlet	<b>coward</b>
<b>sunset</b>	coarse	<b>fever</b>
<b>bless</b>	radiator	<b>germs</b>
<b>luxury</b>	errand	<b>gloom</b>
<b>soothe</b>	scissors	<b>grief</b>
<b>sleep</b>	elbow	<b>hardship</b>
<b>secure</b>	stove	<b>lonely</b>
<b>angel</b>	hammer	<b>obesity</b>
<b>breeze</b>	rattle	<b>poverty</b>
ocean	metal	<b>slum</b>
<b>melody</b>	trunk	<b>stupid</b>
<b>relaxed</b>	taxi	<b>trash</b>
snuggle	theory	<b>waste</b>
bunny	engine	idiot
carefree	finger	fault
intellect	clock	pity
politeness	machine	criminal
peace	history	messy
soft	street	corpse
inspire	swamp	fatigued
rainbow	aloof	mucus
warmth	tool	discomfort

\*Bolded words represent words originally used by Kensinger et al., 2008



- Targets were not significantly different from lures on characteristics, including valence
- Within list, targets were not significantly different on arousal, word length, or semantic relatedness across category (i.e., positive was not significantly different from negative in regards to arousal)

List A

<b>Valence</b>	<b>Target</b>	<b>Lure</b>
Negative	corpse	blister
Negative	coward	bored
Negative	discomfort	criminal
Negative	fatigued	fever
Negative	fault	gloom
Negative	germs	hardship
Negative	grief	idiot
Negative	obesity	lonely
Negative	pity	messy
Negative	poverty	mucus
Negative	slum	stupid
Negative	trash	waste
Positive	bless	angel
Positive	breeze	bunny
Positive	cozy	carefree
Positive	intellect	inspire
Positive	luxury	ocean
Positive	melody	peace
Positive	politeness	rainbow
Positive	reward	relaxed
Positive	secure	sleep
Positive	snuggle	soothe
Positive	soft	useful
Positive	sunset	warmth
Neutral	appliance	aloof
Neutral	clock	elbow
Neutral	coarse	finger
Neutral	engine	hammer
Neutral	errand	history
Neutral	machine	metal
Neutral	radiator	pamphlet
Neutral	rattle	swamp
Neutral	scissors	theory
Neutral	stove	tool
Neutral	street	trunk
Neutral	taxi	utensil

## List B

<b>Valence</b>	<b>Target</b>	<b>Lure</b>
Negative	blister	bored
Negative	corpse	coward
Negative	fault	criminal
Negative	fever	discomfort
Negative	grief	fatigued
Negative	lonely	germs
Negative	mucus	gloom
Negative	obesity	hardship
Negative	pity	idiot
Negative	slum	messy
Negative	trash	poverty
Negative	waste	stupid
Positive	angel	bunny
Positive	bless	carefree
Positive	breeze	inspire
Positive	cozy	luxury
Positive	intellect	melody
Positive	ocean	politeness
Positive	peace	sleep
Positive	rainbow	snuggle
Positive	relaxed	soft
Positive	reward	sunset
Positive	secure	useful
Positive	soothe	warmth
Neutral	coarse	aloof
Neutral	elbow	appliance
Neutral	engine	clock
Neutral	hammer	errand
Neutral	history	finger
Neutral	machine	radiator
Neutral	metal	rattle
Neutral	pamphlet	stove
Neutral	scissors	street
Neutral	swamp	taxi
Neutral	theory	trunk
Neutral	tool	utensil

List C

<b>Valence</b>	<b>Target</b>	<b>Lure</b>
Negative	bored	blister
Negative	corpse	discomfort
Negative	coward	fault
Negative	criminal	germs
Negative	fatigued	gloom
Negative	fever	lonely
Negative	grief	obesity
Negative	hardship	pity
Negative	idiot	poverty
Negative	messy	slum
Negative	mucus	stupid
Negative	trash	waste
Positive	bunny	angel
Positive	cozy	bless
Positive	intellect	breeze
Positive	ocean	carefree
Positive	luxury	inspire
Positive	melody	peace
Positive	relaxed	politeness
Positive	reward	rainbow
Positive	secure	sleep
Positive	snuggle	soft
Positive	sunset	soothe
Positive	warmth	useful
Neutral	aloof	appliance
Neutral	coarse	clock
Neutral	hammer	elbow
Neutral	machine	engine
Neutral	metal	errand
Neutral	pamphlet	finger
Neutral	radiator	history
Neutral	scissors	rattle
Neutral	taxi	stove
Neutral	theory	street
Neutral	tool	swamp
Neutral	utensil	trunk

**Changes made based on piloting:**

N=24 men and women were piloted, with each list piloted once and list B piloted twice after changes were made to the list. List of changes to List B and C:

- Lake was changed for “ocean” after participants noting an average score of 5.0 (SD = 0.0) for the word lake.

- List B: Targets and Lures were switched to equate lists on arousal; ( $p=0.12$  with negative prior to switch); “utensil” and “scissors” were switched.

Initial results:

- Pleasant was recognized significantly higher compared to neutral when examining targets and when examining targets minus false alarms. Unpleasant was not significantly different from neutral, though numerically was slightly higher.
- Tables below are list characteristics after changes made due to piloting procedures. These represent the stimuli used in all groups for the current study.

<b>Entire Word Bank</b>	<b>Pleasant</b>	<b>Neutral</b>	<b>Unpleasant</b>
Valence	7.34 (0.35)	5.03 (0.21)	2.67 (0.52)
Arousal	4.09 (0.72)	4.06 (0.39)	4.13 (0.61)
Word length	6.08 (1.47)	6.04 (1.30)	5.92 (1.47)
Frequency	26.98 (47.60)	24.56 (34.92)	26.15 (42.19)

<b>List A – Targets</b>	<b>Pleasant</b>	<b>Neutral</b>	<b>Unpleasant</b>
Valence	7.35 (0.37)	4.97 (0.23)	2.59 (0.60)
Arousal	4.25 (0.609)	4.00 (0.36)	4.20(0.63)
Word length	6.25 (1.76)	6.33 (1.44)	6.09 (1.75)
Semantic Relatedness	0.118	0.108	0.110

<b>List B – Targets</b>	<b>Pleasant</b>	<b>Neutral</b>	<b>Unpleasant</b>
Valence	7.32 (0.41)	5.04 (0.22)	2.71 (0.53)
Arousal	3.98 (0.84)	4.17 (0.40)	4.21 (0.43)
Word length	5.83 (1.40)	6.08 (1.24)	5.33 (0.98)
Semantic Relatedness	0.114	0.106	0.104

<b>List C – Targets</b>	<b>Pleasant</b>	<b>Neutral</b>	<b>Unpleasant</b>
Valence	7.36 (0.38)	4.96 (0.22)	2.78 (0.48)
Arousal	4.03 (0.79)	4.06 (0.41)	4.00 (0.77)
Word length	6.00 (1.35)	6.16 (1.47)	5.92 (1.31)
Semantic Relatedness	0.110	0.099	0.103

Piloting in HD patients ( $n=4$ ) indicated that 4s was an appropriate exposure time to allow patients enough time to respond. Qualitatively, patients reported having enough time to read the word and make a selection, which was also observed by the examiner. The median words missed during the encoding trial was one word, with one subject having difficulty knowing which button to press. As such, an additional trial was added to the directions as a result of this difficulty. This required participants to press a button on command (i.e., “press the button for unpleasant”).

## APPENDIX E: CONTROL TASK PILOTING AND WORD LISTS

**Background:** Word frequency and ambiguity have been suggested to impact “lexical access” and therefore altering the way in which words are remembered (Rayner & Duffy, 1986). Low frequency words have been found to be more accurately recognized than high frequency items across several studies (Rugg, Cox, Doyle, & Wells, 1995; MacLeod & Kampe, 1996). In free recall, when presented with mixed lists (i.e., interspersed high and low frequency words), the typical high-frequency easier-recall effect was reversed where rare words were recalled more efficiently than common words (May & Tryk, 1970). Further, expectation of recall did not negatively impact recognition of low frequency words (Balota & Neely, 1980), which was important in the current study since this task occurred after the emotional memory task.

**Method:** High frequency was defined as with frequencies above 100 per million (consistent with DeLosh et al., 1996), with low frequency defined as less than 3 per million (consistent with Balota et al 1980), and 20 middle frequency words between 20 and 35 per million were used as lures in the recognition task. Several methods were examined, including list length (14 per category vs 10 per category) and delay (10 seconds vs 90 seconds).

<b>High Frequency Word</b>	<b>Letter length</b>	<b>Frequency (SUBTLWF)</b>	<b>Low Frequency Word</b>	<b>Letter length</b>	<b>Frequency (SUBTLWF)</b>
change	6	240.35	babble	6	0.86
excuse	6	368.1	bleach	6	2.31
minute	6	377.49	cork	4	2.86
need	4	1294.9	crumb	5	1.8
part	4	261.51	hiccup	6	0.53
point	5	236.53	knuckle	7	1.29
president	9	140.67	merge	5	1.39
stop	4	707.27	slurp	5	0.43
wait	4	830.25	sway	4	2.53
work	4	798.02	zigzag	6	0.45
<b>AVERAGE</b>	<b>5.2</b>	<b>525.51</b>	<b>AVERAGE</b>	<b>5.4</b>	<b>1.45</b>

Note: HF= High frequency, LF = low frequency; Frequency from Brysbaert & New (2009).

	<b>HF Recog %</b>	<b>LF Recog %</b>	<b>False alarm %</b>	<b>HF Recall %</b>	<b>HF Recall %</b>
10 words (n=7)	0.77	0.95	0.09	0.45	0.60
14 words (n=6)	0.69	0.87	0.33	0.18	0.23

Recognition was significantly higher for recognition for lists 10 per category ( $p < 0.001$ ) and lists of 14 per category ( $p < 0.05$ ). False alarms were significantly higher in the 14 word conditions ( $p < 0.05$ ).

<b>Lure words</b>	<b>Letter length</b>	<b>Frequency (<i>SUBTLWF</i>)</b>
cheap	5	36.24
dirt	4	25.69
fate	4	26.96
freeze	6	32.16
giant	5	27.06
mile	4	21.00
mystery	7	22.96
parking	7	27.04
pretend	7	40.31
repeat	6	33.02
series	5	20.16
shadow	6	21.18
silent	6	23.00
skip	4	21.10
switch	6	28.12
total	5	37.65
vote	4	34.33
warn	4	25.35
winter	6	26.22
chain	5	21.22
<b>AVERAGE</b>	<b>5.3</b>	<b>27.54</b>

Note: Frequency from Brysbaert & New (2009)