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Autobiographical Memory in Huntington's Disease

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Abstract

Huntington's disease (HD) is a hereditary neurodegenerative disorder recognised by hallmark progressive motor symptoms, including chorea, which manifest around midlife. In addition to motor symptoms, cognitive decline and neuropsychiatric sequelae are clinical features of HD. Deficits in memory retrieval and recognition have been detected in HD gene-expansion carriers who are estimated to be at least 10 years prior to the current diagnostic threshold (or people with *premanifest*-HD). Most studies yielding evidence of memory deficits in HD have emerged from word-list learning tasks. Few studies have examined more ecologically relevant tests of memory in premanifest or manifest HD samples, and no published research to date has investigated autobiographical memory. Autobiographical memory involves personally experienced events from the lifetime and acquired knowledge and facts about a person's own life. Autobiographical memory dysfunction is a common feature of other neurodegenerative disorders including Alzheimer's disease and frontotemporal dementia. Dysfunction of autobiographical memory in neurodegenerative disorders has been linked to reduced sense of self continuity and personal identity, which are known to be important for quality of life and sense of personal autonomy in adulthood. These failures in autobiographical memory are typically attributed to hippocampal degeneration and broader temporal lobe and frontal pathology associated with these disorders. More recently, research has detected autobiographical memory failure in traumatic brain injury populations pointing to a possible association between striatal volumes and the retrieval of personally salient autobiographical memories.

The overall aim of the studies presented in this thesis was to determine autobiographical memory integrity, function, and neural underpinnings in HD. We collected data from a sample of participants with late-premanifest HD, early stage HD and healthy controls. The number of participants in each study in this thesis varies slightly as not all

participants completed the autobiographical memory task (presented in Chapter 3 and 4) or the neuroimaging data collection (presented in Chapter 4).

The testing protocol for the studies presented in this thesis included a series of cognitive tasks to assess general neuropsychological function and estimate premorbid intellectual abilities. Participants completed the Autobiographical Interview, which is a semi-structured interview to assess autobiographical memory across different life epochs. A questionnaire (the Thinking About Life Scale – Revised) was used to assess the functions of autobiographical memory. Participants also underwent magnetic resonance imaging (MRI) scanning, which included structural (T1-weighted) imaging, resting state functional MRI (fMRI), and diffusion tensor imaging (DTI). Only results from the structural MRI are reported in this thesis, which were used to determine volumes of striatal and hippocampal structures.

A number of significant findings emerged from these investigations; these are documented in Chapters 3 to 5. First, we found that both late premanifest HD and manifest HD participants demonstrated pervasive impairments in episodic autobiographical memory retrieval. Second, we found associations between striatal atrophy and episodic autobiographical memory impairments in both free and probed recall of autobiographical memories, supporting emerging evidence for a possible role of striatal regions in autobiographical memory. Third, we found emerging evidence that people with manifest HD self-report using their autobiographical memories less frequently for social reasons such as to bond with others or to foster intimacy in relationships.

Taken together, the findings presented in this thesis provide novel insights into the cognitive phenotype of HD and strengthen previously purported evidence for striatal involvement in autobiographical memory function. In addition, our findings provide initial evidence of the impact that impaired autobiographical memory function may have on

reminiscence behaviours in HD. Longitudinal studies are essential to understanding the rate of deterioration of autobiographical memory in HD. Examining DTI and resting state fMRI correlates of autobiographical memory are also needed future directions to further understand the relationship between HD pathology and autobiographical memory. Finally, we suggest that investigating the personal impact that autobiographical memory dysfunction has on people with HD will assist us in developing possible therapeutic and clinical interventions to improve quality of life for people living with this currently incurable disease.

Publications and Presentations During Enrolment

Journal Articles

Carmichael, A. M., Irish, M., Glikmann-Johnston, Y., Singh, P., & Stout, J. C. (2019). Pervasive autobiographical memory impairments in Huntington's disease. *Neuropsychologia*, *127*, 123-130. doi: 10.1016/j.neuropsychologia.2019.02.017

Conference Poster Presentations

Carmichael, A. M., Glikmann-Johnston, Y., Irish, M., Stout, J. C. (2018). Autobiographical memory in premanifest and manifest Huntington's disease. Poster presented at NHMRC National Institute for Dementia Research Australian Dementia Forum in Sydney, Australia, June 4th-5th 2018.

Carmichael, A. M., Glikmann-Johnston, Y., Irish, M., Stout, J. C. (2018). Autobiographical memory in Huntington's disease. Poster presented at the International Neuropsychology Society 46th Annual Meeting in Washington, USA, February 14th-18th 2018.

Conference Oral Presentations

Carmichael, A. M., Irish, M., Glikmann-Johnston, Y., Singh, P. Stout, J. C. (December, 2018). Pervasive autobiographical memory impairments in Huntington's disease. Platform presentation at Huntington's Research Day in Melbourne, Australia.

Award: Best Student Presentation

Thesis Including Published Works Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes one original paper published in peer reviewed journal, one paper revised and resubmitted in a peer reviewed journal, and one paper submitted and under review in a peer reviewed journal. The core theme of the thesis is Autobiographical memory in Huntington's disease. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the School of Psychological Sciences under the supervision of Professor Julie Stout, A/Prof Muireann Irish, and Dr Yifat Glikmann-Johnston.

(The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.)

In the case of Chapters 3-5 my contribution to the work involved the following:

Thesis Chapter	Publication Title and Status	Nature and % of student contribution	Nature and % of co-authors' contribution
3	Pervasive autobiographical memory impairments in Huntington's disease. *Published in Neuropsychologia*	70%. Design of study protocol, ethics, recruitment and data collection. Data analysis and interpretation. Preparation of manuscript.	1) Prof Julie Stout: Provided advice on study design and interpretation of findings. Provided feedback on manuscript, 10% 2) A/Prof Muireann Irish: Provided advice on interpretation of results, structure of discussion, and feedback on manuscript, 10% 3) Dr Yifat Glikmann-Johnston: Provided advice on data recruitment and feedback on manuscript, 5% 4) Mr Paldeep Singh: Provided reliability (coding) for autobiographical interviews and review of manuscript, 5%
4	Striatal and hippocampal correlates of autobiographical memory in Huntington's disease. *Under Review in Cortex*	70%. Design of study protocol, ethics, recruitment and data collection. Data analysis and interpretation. Preparation of manuscript.	1) Prof Julie Stout: Provided advice on study design and interpretation of findings. Provided feedback on manuscript, 10% 2) Dr Yifat Glikmann-Johnston: Provided advice on data recruitment, imaging analysis, guidance regarding

			data analysis and feedback on manuscript, 10% 3) A/Prof Muireann Irish: Provided advice on interpretation of findings. Provided feedback on manuscript, 5% 4) Dr Bonnie Alexander: Provided imaging assistance including pre-processing and extracting automated volumes, 2.5% 5) Ms Emily Claire Mercieca: Assisted with imaging analysis and recruitment, 2.5%
5	Discrete changes in the frequency and functions of autobiographical reminiscence in Huntington's disease. *Revised and resubmitted in Memory.*	75%. Design of study protocol, ethics, recruitment and data collection. Data analysis and interpretation. Preparation of manuscript.	1) Prof Julie Stout: Provided advice on study design and interpretation of findings. Provided feedback on manuscript, 10% 2) A/Prof Muireann Irish: Provided advice on interpretation of findings. Provided feedback on manuscript, 10% 3) Dr Yifat Glikmann-Johnston: Provided advice on data recruitment, guidance regarding data analysis and feedback on manuscript, 5%

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: **Date:** 27-July-2019

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: **Date:** 27-July-2019

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We made it!

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Abbreviations

AI	Autobiographical Interview
AMI	Autobiographical Memory Interview
CAG	Cytosine Adenine Guanine
CESD-R	Center for Epidemiological Studies Depression Scale Revised
CT	Computed Tomography
DBS	Disease Burden Score
DTI	Diffusion Tensor Imaging
fMRI	Functional Magnetic Resonance Imaging
FSIQ	Full-Scale Intelligence Quotient
HD	Huntington's Disease
HIV	Human Immunodeficiency Virus
HTT	Huntingtin Protein
IQ	Intelligence Quotient
MNI	Montreal Neurosciences Institute
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NART	National Adult Reading Test
PRE-HD	Premanifest Huntington's disease
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
RFS	Reminiscence Functions Scale
ROI	Region of Interest
SDMT	Symbol Digit Modalities Test
TALE-R	Thinking About Life Scale - Revised

TFC	Total Functional Capacity
TMS	Total Motor Score
TMT	Trail Making Test
UHDRS	Unified Huntington's Disease Rating Scale
VBM	Voxel Based Morphometry

Preface

Huntington's disease (HD) is a hereditary neurodegenerative disorder with devastating and progressive cognitive, neuropsychiatric and motor symptoms. Memory deficits have been detected in HD gene-carriers 10-15 years prior to when the disease is considered clinically manifest. Despite cognitive and neuropsychiatric symptoms emerging prior to motor signs in HD, motor symptoms remain the current diagnostic basis. Memory deficits in HD tend to emerge from classic word-list or story learning tasks. No published research, to our knowledge, has investigated autobiographical memory function in HD. Autobiographical memories are memories of events and personal facts amassed across the lifespan. Understanding autobiographical memory function and integrity in HD will allow a deeper understanding of the cognitive phenotype of HD, as well as the lived experience of someone with the disorder.

As such, the objective of my thesis was to further our understanding of the memory profile of premanifest and manifest HD, by investigating autobiographical memory. We investigated autobiographical memory in HD from a cognitive, neural and functional perspective. We asked 'what' people living with HD can remember from their lives, 'how' autobiographical memory dysfunction relates to neuropathology associated with the disease, and 'why' people living with HD use their autobiographical memories on a daily basis. By integrating cognitive, neuroimaging and functional methods in this thesis, we were able to provide novel insights into memory function and utility in HD that we hope will assist in tailoring psychosocial support and interventions for people living with HD.

With respect to the structure of this thesis, Chapter 1 provides a general overview. The overview begins by discussing cognition in HD, focusing on memory function. We also provide a broad overview of autobiographical memory. In the absence of any previous research on this topic in HD, we focus here on previous work in ageing and

neurodegenerative populations, as well as the neural underpinnings of autobiographical memory function. Finally, we focus on how and why people use their autobiographical memories on a daily basis by discussing reminiscence. Each section of the introduction (Chapter 1) includes a summary section to aid readability. Chapter 2 is an overview of the methodology employed in this thesis. This chapter focuses on a more detailed description of the Autobiographical Interview (AI) task used in the study as well as the manual tracing protocols used for neuroimaging component of this thesis.

Experimental papers are presented in Chapter 3, Chapter 4, and Chapter 5. Chapter 3 is the main paper on autobiographical memory in HD, and it details the integrity of autobiographical memory across life epochs in premanifest and manifest HD. Chapter 4 examines the neural underpinnings of autobiographical dysfunction in HD by carefully examining the volumes of the caudate, putamen, and hippocampus using manual tracing techniques applied to images from magnetic resonance imaging (MRI). Chapter 5 details the functions, or reasons, that people living with HD report using their autobiographical memory on a daily basis.

Finally, Chapter 6 is an integrated discussion of the main findings from this thesis, including implications of this research, both for the HD literature, and the autobiographical memory literature, respectively. Given the thesis is formatted by the three publications, some unavoidable repetitions of materials are included in the introductory chapter (Chapter 1) and subsequent introduction sections for each manuscript. To guide the reader of the thesis, explanatory notes precede each manuscript (Chapter 3-5) to provide additional rationale and further clarification and linkage between chapters.

CHAPTER 1: INTRODUCTION

1.1 Huntington's Disease (HD)

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded trinucleotide repeat (CAG) affecting the IT15 gene on chromosome 4. This expansion causes the huntingtin protein (HTT) to mis-fold and accumulate, leading to neuronal dysfunction and cell death (Li & Li, 2004). The incidence of HD is estimated to be 5-10 cases per 100,000 people world-wide. A recent meta-analysis of prevalence studies reported that in Australia the incidence of HD is approximately 5.63 per 100,000 people (Rawlins et al., 2016). HD symptoms typically emerge in middle-adulthood, however juvenile and geriatric onset can also occur. There is currently no cure for HD, and the expected life span of someone with HD is estimated to be 15-20 years after symptoms emerge (Ross & Tabrizi, 2011). Current estimates suggest that approximately 60% of the variance in the age when the clinical phenotype of HD emerges is related to the length of the CAG repeat, with longer trinucleotide repeat lengths linked to earlier disease manifestation (Wexler, 2004). For example, CAG repeat lengths of 40 or more are associated with almost full penetrance by 65 years of age (Langbehn et al., 2004). The clinical phenotype of HD includes a heterogeneous presentation of motor dysfunction, neuropsychiatric symptoms, and cognitive decline.

Motor disturbances are the hallmark symptom of HD. The current diagnostic basis of the disease as manifest (Huntington Study Group, 1996) is the unequivocal evidence of chorea consistent with HD, in conjunction with a genetic test confirming CAG expansion of 39 or greater. Extrapyramidal motor signs of HD include chorea, rigidity, incoordination, postural instability, and bradykinesia. Chorea is the most outwardly apparent feature of HD, and it involves involuntary, irregular and complex muscle movements. Chorea, along with slowed movements (bradykinesia) and incoordination occur in early stages of HD, whereas rigidity typically causes more functional impairment in the late stages of the disease

(Rosenblatt et al., 2003). When a person is confirmed to have the HD CAG expansion (via predictive testing) but is yet to exhibit motor symptoms meeting the threshold for diagnosis, they are referred to in the literature as being in the 'presymptomatic' or 'premanifest' stage of HD. I refer to this stage as premanifest HD throughout this thesis for consistency, due to known cognitive and neuropsychiatric symptoms that emerge prior to the current diagnostic threshold of HD.

Neuropsychiatric signs in HD are common but vary across individuals and the course of the disease. Specifically, signs can include apathy, depression, irritability, agitation, dysphoria and anxiety. A cross-sectional study of caregivers of people with manifest HD found that over 50% of caregivers reported that they observed dysphoria, agitation, irritability, apathy or anxiety in the person they were caring for with HD over a month-long period, demonstrating the pervasiveness of these symptoms (Paulsen, Ready, Hamilton, Mega, & Cummings, 2001). Neuropsychiatric findings occur not only in people with clinical diagnosis of HD, but have also been reported in premanifest HD. For example, Duff and colleagues (2007) compared self-reported psychiatric symptoms in people with premanifest HD to people without the HD CAG expansion. They found that people with premanifest HD reported elevated symptoms in several psychiatric domains, including depression, hostility, obsessive-compulsive tendencies, and anxiety. This was an important finding, because these symptoms were observed prior to diagnosis in people both near, and far, from estimated onset, which highlights the long neuropsychiatric prodromal period that can occur in the lead up to when HD is considered manifest. Adding further evidence to the pervasiveness of neuropsychiatric symptoms in HD across the course of the disease, a longitudinal study by Thompson and colleagues (2012) showed that apathy, depression and irritability were prevalent in their sample. Whereas many neuropsychiatric symptoms appear and resolve

during the course of HD, apathy was found to increase with disease progression (Thompson et al., 2012).

Of particular relevance to this thesis, in addition to neuropsychiatric symptoms, cognitive signs have been detected in HD at least ten years prior to diagnosis (Stout et al., 2011). These symptoms worsen with disease progression eventually resulting in a dementia syndrome. Early cognitive deficits in HD include executive dysfunction, memory impairment, slowed processing speed, emotion recognition and visuospatial dysfunction. Executive functioning deficits in HD include reduced verbal fluency and attention, and impaired organisation and planning skills (Craufurd & Snowden, 2002). Both visuospatial memory and episodic verbal memory deficits have been detected in premanifest HD, with deficits worsening with disease progression (Solomon et al., 2007; Stout et al., 2011). Emotion recognition deficits, considered to be within the cognitive symptomatology of HD, have also been identified in HD (Kempnich et al., 2018). As a whole, our understanding of the cognitive burden of HD, particularly in the premanifest and early manifest stages continues to improve as a result of evidence accumulated from longitudinal studies, large observational studies, and neuroimaging research.

Motor, neuropsychiatric and cognitive symptoms of HD are associated with declines in quality of life (Read et al., 2013). The impact of HD is significant within family systems due to the hereditary, autosomal dominant nature of the disease, which means that often several members of a family are affected simultaneously, and in multiple generations. Recent evidence suggests that quality of life deteriorates with disease progression, with those in later stages of the disease reporting lower quality of life across physical, emotional and social domains compared to people without the disease (Read et al., 2013). The potential for psychosocial interventions in HD has not been examined, with very minor exceptions, and with the development of appropriate therapeutic approaches would be very beneficial for

people with HD to maintain quality of life. In addition to quality of life studies, the broader impact on families living with HD has been studied, although only minimally. Jona et al. (2017) reported that family members of people diagnosed with HD felt that affective involvement (e.g., interest in one another's emotional experience) and communication were the most disrupted in their families. Consistent with these quantitative findings, a qualitative study by Hartelius et al. (2010) found that family members of people diagnosed with HD reported a deterioration in communication and need for more supports. Taken together, these studies demonstrate the ripple effects that HD has beyond the individual, and the burden of the disease on the wider family and support system.

Summary. HD is a hereditary neurodegenerative disorder with devastating and progressive cognitive, neuropsychiatric and motor symptoms. In Australia, HD is estimated to affect approximately 5.63 per 100,000 people (Rawlins et al., 2016), and there is currently no cure. The impact of HD is significant within family systems due to the hereditary, autosomal dominant nature of the disease, which means that often several members of a family are affected simultaneously, and in multiple generations. Most clinical features and symptoms of premanifest and manifest HD discussed in this section of the thesis can be attributed to degeneration and atrophy of the central nervous system (Ross & Tabrizi, 2011), and thus understanding the neuropathology of HD is crucial.

1.1.2 Neuropathology of HD. Neuropathological progression of HD has been increasingly studied since the disease was first discovered, and is thought to underlie most clinical signs and symptoms in HD. An important early study by Vonsattel and colleagues (1985), which examined 163 brains post-mortem, developed the seminal neuropathological classification of HD. This research was crucial to modern understanding of the neuropathology of HD as it confirmed progressive degeneration of the caudate and putamen regions and provided a grading system to quantify the severity of atrophy in HD. Since this

early research, imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), have allowed further characterisation and understanding of patterns of atrophy in HD, enabling researchers to investigate neuropathological changes *in vivo* in premanifest and manifest HD.

In addition to the well-documented early and striking atrophy disproportionately affecting the striatum in HD, additional new findings continue to emerge, detailing the changes occurring outside of the striatum. With disease progression, grey matter atrophy becomes more global, affecting brain regions beyond striatal structures, including the thalamus, hippocampus, amygdala, cerebral grey matter, and the cerebellum in manifest HD (Georgiou-Karistianis, Scahill, Tabrizi, Squitieri, & Aylward, 2013; Jernigan, Salmon, Butters, & Hesselink, 1991; Rosas et al., 2003; Vonsattel et al., 2011). Examining these extra-striatal changes allows a better understanding of the mechanisms that may underlie cognitive signs and symptoms throughout the premanifest and manifest stages of HD. For example, reductions in amygdala volumes have been reported in premanifest HD from both cross-sectional (Ahveninen, Stout, Georgiou-Karistianis, Lorenzetti, & Glikmann-Johnston, 2018; Douaud et al., 2006; Majid et al., 2011; Mason et al., 2015; Thieben et al., 2002) and longitudinal studies (Majid et al., 2011). Studies correlating amygdala volume and clinical outcomes have yielded mixed results, with some studies finding evidence for links between amygdala volume and mood (Ahveninen et al., 2018), whereas others have failed to detect a relationship between volume and emotion recognition (Henley et al., 2008; Scahill et al., 2013). Similarly, evidence regarding hippocampal integrity in premanifest HD has been somewhat mixed, with some studies detecting no differences between premanifest HD and controls (Majid et al., 2011; Possin et al., 2017), while others report subtle volume reductions in people with late premanifest HD as they get closer to the threshold for clinical diagnosis (Faria, Liang, Miller, & Mori, 2017; van den Bogaard et al., 2011). Despite mixed findings

for the presence of hippocampal atrophy in premanifest HD, hippocampal volume has been found to correlate with certain clinical outcomes in HD such as the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score (TMS) and Total Functional Capacity (TFC; Huntington Study Group, 1996; Jech et al., 2007; van den Bogaard et al., 2011). The extent of hippocampal atrophy in HD is important to clarify in order to understand its potential role in cognitive and memory functions in HD. After reviewing the literature, it has emerged that the disparity in findings to date around the integrity of hippocampal volume in HD may be due to several factors including differences in disease stages of premanifest samples (far vs close to diagnosis), sample size effects, and techniques used to estimate hippocampal volumes.

Many techniques have been utilised to estimate volume of grey matter structures in HD, including manual segmentation (Ahveninen et al., 2018; Aylward et al., 2000), semi-automated segmentation (Hobbs et al., 2009), and automated segmentation (Kassubek, Juengling, Ecker, & Landwehrmeyer, 2004; Thieben et al., 2002). Manual tracing of grey matter structures in HD has been utilised as a way to overcome inconsistencies that can occur through automated tracing techniques. Manual segmentation involves an expert rater tracing the outline of a structure on each 'slice' of the MR image using a validated protocol to determine boundaries of the structure (Hobbs et al., 2009). Manual segmentation is considered a valuable method for volumetric quantification of brain structures (Pardoe, Pell, Abbott, & Jackson, 2009), but the expert training involved in learning to trace grey matter structures, paired with the difficult and time consuming nature of carrying out this type of imaging analysis, do not always make this a feasible option for large-scale or longitudinal studies (Schoemaker et al., 2016). Lending support to the use of manual tracing techniques when time and expertise permits, comparison of manual and automated techniques of estimating grey matter volumes, particularly in the hippocampi, have yielded results

suggesting that there are large discrepancies between manual and automated segmentation in neurodegenerative populations with moderate-to-severe brain atrophy and that automated techniques may overestimate structure volume (Sánchez-Benavides et al., 2010). As such, time and expertise permitting, manual tracing of grey matter structures in HD is a useful technique that can assist with avoiding over-estimating neural volumes and avoiding automated errors that can occur when delineating regional boundaries in highly atrophic brains.

In addition to the well-described grey matter atrophy in HD, pathological changes in white matter pathways have been proposed as a possible mechanism underlying early cognitive and motor changes in HD (Li & Conforti, 2013). In particular, those pathways that connect the striatum to other parts of the brain are likely to have particular significance in HD. Using diffusion tensor imaging (DTI), which examines the location and orientation of white matter pathways in the brain by measuring the diffusion of water molecules, researchers have detected white matter changes in both premanifest and manifest HD (Dumas et al., 2012; Klöppel et al., 2008; Rosas et al., 2010; Rosas et al., 2006). Poudel and colleagues (2014) found reduced white matter connectivity and microstructural changes in the network connecting the putamen with prefrontal and motor cortices in premanifest HD, whereas manifest HD showed more diffuse impairment to networks connecting frontal and parietal cortices with both the caudate and the putamen.

Recent advances in the ability to study the neural substrates of HD have amassed to form a collection of evidence suggesting that dysfunction in HD involves a combination of grey and white matter degradation, which progresses with disease course, and disrupts the efficiency and execution of cognitive operations. From a clinical and research perspective, neuroimaging can also be useful for identifying biomarkers of the disease progression, such as caudate degeneration (Aylward, 2007), which is particularly helpful considering, as

previously mentioned, measures of disease progression and disease burden estimates in HD (such as using the CAG length to predict age of onset) are not very precise, only accounting for around 60% of variance in disease onset (Wexler, 2004).

Summary. From a neuropathological perspective, HD is characterised by progressive and widespread neural changes including early and striking degeneration that disproportionally affects striatal regions (i.e., caudate, putamen). Extra-striatal atrophy in grey matter regions have been reliably observed in manifest HD, with more mixed-evidence for atrophy in premanifest HD (Vonsattel et al., 2011). Pathological changes have also been detected in white-matter integrity, including reduced fronto-striatal connectivity (e.g., Dumas et al., 2012; Poudel et al., 2014). Taken together, the literature highlights the utility of incorporating neuroimaging techniques in conjunction with behavioural measures of cognitive performance to allow a deeper understanding of cognition across the disease-course of HD.

1.2 Memory in HD

The last 3-4 decades have seen an enormous increase in our understanding of memory in HD, which has been aided significantly by the discovery of the HD CAG expansion and by large observational studies. Memory in HD is the focus of this thesis, and as such we have thoroughly reviewed existing literature here. Beyond HD and within the cognitive neuroscience literature, understanding of memory processes in general has also vastly grown in parallel over the past 30-40 years. Within memory literature, long-term memory is typically fractioned into implicit (non-declarative) and explicit (declarative) components. Implicit memories are acquired and retrieved unconsciously (Graf & Schacter, 1985; Schacter, 1987), whereas explicit memory facilitates conscious, intentional recollection of factual information, experiences and concepts (Tulving, 1985). The distinction between these two memory systems was described in practical terms by Schacter (1987, p.501) using task

performance. He wrote: "…implicit memory is revealed when previous experiences facilitate performance on a task that does not require conscious or internal recollection of those experiences; explicit memory is revealed when performance on a task requires conscious recollection of previous experiences".

1.2.1 Implicit memory. The current thesis focuses on explicit memory in HD, and more specifically autobiographical memory, however we have briefly summarised findings regarding implicit memory in HD to provide a more comprehensive picture of memory functioning in HD, including what is known, and what warrants further investigation. Traditional models portray implicit memory as a process that is not dependent on the medial temporal lobe memory system (Squire, Stark, & Clark, 2004). Rather, the caudate, putamen, prefrontal cortex, primary and supplementary motor cortices, and the anterior cingulate cortices have all been implicated in the implicit memory system (Brown, Redondo-Verge, Chacon, Lucas, & Channon, 2001; Schneider et al., 2010). Implicit memory includes motor-based learning, priming and perceptual learning (Squire et al., 2004). Motor-based implicit memory is thought to be underpinned by the striatal regions, whereas priming and perceptual learning relies more heavily on the neocortical regions of the brain (Squire et al., 2004). Due to the relevant pathology of HD, including striking early atrophy in the striatal regions, motor-based implicit memory has received the most empirical attention within the implicit memory literature.

Motor-based (procedural) implicit memory includes collections of coordinated movements and skills that allow people to carry out both simple and complex everyday tasks, such as stirring a pot of soup, chewing food, or riding a bicycle. This type of motor sequence (skill) learning has been found to be impaired in early stage manifest HD (Heindel, Butters, & Salmon, 1988; Heindel, Salmon, Shults, Walicke, & Butters, 1989). Gabrieli, Stebbins, Singh, Willingham, and Goetz (1997) further supported these findings of impaired skill

learning, by showing that people with manifest HD were impaired on a rotary-pursuit task involving them to hold a stylus and maintain contact with a rotating spot. There is some evidence that motor sequence learning may be intact in premanifest HD (Schneider et al., 2010), however this research has been limited by small sample sizes. The identification of impaired motor sequence (skill) learning in HD has important functional implications for someone living with HD, due to the potential for impaired motor sequence learning to impede the ability to complete tasks that are integral to daily activities and personal independence (i.e., the ability to chew and swallow food without choking; Paulsen, 2011).

Priming, which is the unconscious expression of recently encountered material, has been found to be relatively intact in manifest HD (Shimamura, Salmon, Squire, & Butters, 1987). Similarly, perceptual learning, by which the ability to respond to sensory stimuli in the environment is improved through experience, is also thought to be relatively intact in manifest HD (Maki, Bylsma, & Brandt, 2000).

Summary. Implicit memory is described as memories that are acquired and retrieved unconsciously (Graf & Schacter, 1985; Schacter, 1987). Implicit memory includes motor-based learning, priming and perceptual learning (Squire et al., 2004). Motor-based implicit memory is thought to be underpinned by the striatal regions, whereas priming and perceptual learning relies more heavily on the neocortical regions of the brain (Squire et al., 2004). Studies have demonstrated that motor-based implicit memory is impaired in HD, which is likely due to pronounced atrophy in the striatal regions that occurs in HD, whereas other types of implicit memory thought to be dependent on neocortical regions are believed to be relatively intact in HD. There remains a relative dearth of published studies investigating implicit memory in premanifest HD.

1.2.2 Explicit memory. The integrity of explicit memory in HD has received considerable empirical attention. Based on Tulving's (1985) definition, explicit memory can

be divided into semantic and episodic components, although current understanding suggests that these two forms of memory are not completely distinct. *Semantic memory* can be defined as facts and knowledge amassed across the lifetime not bound to a specific time or place, whereas *episodic memory* is information from a specific time and place. Both semantic and episodic memories can be autobiographical in nature or non-autobiographical (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). We focus on semantic and episodic autobiographical memory later in the introduction chapter of this thesis and review the state of non-autobiographical explicit memory in HD here.

Semantic memory refers to our memory for generic knowledge and facts in the absence of context such as time and place (Martin & Chao, 2001). Semantic memory encompasses all the declarative knowledge we acquire about the world, including our ability to remember the names of all objects we know in our environment, as well as underpinning our understanding of language (Binder & Desai, 2011). Semantic memory can be difficult to measure in a laboratory setting, due to its relatively ambiguous and broad definition, however several key studies have reported on the integrity of semantic memory in HD. Early research by Hodges, Salmon and Butters (1990) used language tests thought to tap into semantic knowledge stores to investigate semantic memory integrity in HD, including picture naming tasks and category and letter fluency tasks. Hodges et al. (1990) reported that people with HD showed impairments on all tasks compared to controls *but* demonstrated relatively poorer performance on an executively driven task (i.e., letter fluency) compared to more semantic-based task (i.e., category fluency). From these findings, the authors concluded that executive impairments in HD may be the cause of poorer performance on semantic tasks, rather than reduced semantic knowledge *per se*. More recent studies have employed similar experimental tasks to Hodges et al. (1990), including letter and category fluency tasks, to investigate semantic memory in HD, yielding a similar pattern of findings and interpretation. For

example, Ho and colleagues (2002) reported that semantic category fluency was relatively intact in HD. In summary, semantic memory is often reported as intact in HD, but an extensive search of the literature reveals that the number of studies specifically examining semantic memory in HD (using robust testing batteries) remains reasonably limited.

In contrast to the literature on semantic memory, the study of episodic memory has received far more empirical attention in HD. The majority of our knowledge of episodic memory systems in HD comes from classic word-list and story learning tasks. Examples of commonly used neuropsychological measures used to quantify verbal episodic memory were described by Montoya and colleagues in their 2006 meta-analysis examining episodic memory in HD and includes the following measures: Hopkin's Verbal Learning Test, California Verbal Learning Test, Rey Auditory Verbal Test, and Logical Memory from the Wechsler Memory Scale. Similarly, Visual Production from the Wechsler Memory Scale and the Rey Complex Figure Test are regularly used to assess visual aspects of episodic memory. Although we focus on verbal episodic memory below, it is important to note that impairments on visual memory tasks have been consistently reported in both manifest HD (Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Lawrence, Watkins, Sahakian, Hodges, & Robbins, 2000) and premanifest HD (e.g., Dumas, Van Den Bogaard, Middelkoop, & Roos, 2013; Glikmann-Johnston, Carmichael, Mercieca, & Stout, 2019).

Verbal episodic memory deficits have been described in the literature over the past 40 years, since early studies by Butters and colleagues (1978) and Caine and colleagues (1977) first investigated memory loss in people with manifest HD. Early research identified impairments in the free-recall of episodic verbal information with relatively spared recognition memory (Butters, Wolfe, Martone, Granholm, & Cermak, 1985), however this theory has shifted over time. A meta-analysis by Montoya and colleagues (2006) extracted data from a selection of studies that investigated episodic memory in HD from 1986 to 2004,

reporting impairments in both recognition and recall memory of people with manifest HD and minor impairments in recall (but not recognition) in premanifest HD. Thus, the previously held theory that memory dysfunction in HD represented a disorder of 'retrieval deficit' has been largely reconsidered since this time, and the idea is gaining traction that instead, episodic memory in HD is characterised as a primary memory failure resulting in an amnesic profile. Although early studies investigating episodic memory set the foundation for our current knowledge of memory function in HD, these studies were limited by several factors including a) absence of genetic testing to confirm presence of HD CAG expansion b) generally small sample sizes, c) and limited representation of participants with premanifest HD *far* from diagnosis.

Since the seminal studies of memory in HD, our understanding of episodic memory in HD has advanced rapidly as a consequence of large-scale observational trials. Having access to large samples of people genetically confirmed to have the HD CAG expansion, has allowed subtle dysfunction in memory systems to be detected and has thus added to our understanding of the neural basis of memory dysfunction throughout the progression of the disease particularly in the premanifest stage. Solomon and colleagues (2007) utilised baseline data from the PREDICT-HD study, including 479 participants from Australia, Canada, and the United States of America, to investigate verbal episodic memory in premanifest HD. Solomon et al. (2007) reported impairments on the free recall components of a verbal word-list learning task in premanifest HD. Further, these researchers found that smaller striatal volumes were associated with lower total learning and recognition scores (Solomon et al., 2007). Stout and colleagues (2011) utilised a larger sample of HD premanifest gene-carriers (n=738), also from the PREDICT-HD study to investigate various neurocognitive performances, finding HD gene carriers in the premanifest stage predicted to be "near" diagnosis (within 9 years) and "mid" way from diagnosis (9-15 years) based on a formula

from Langbehn et al. (2004) showed poorer delayed recall and recognition discriminability compared to controls. HD gene carriers far from diagnosis (15+ years) did not differ significantly from healthy controls (Stout et al., 2011).

Summary. Explicit memory facilitates conscious, intentional recollection of factual information, experiences and concepts (Tulving, 1985). The past 40 years of research has identified that people with the HD CAG expansion show episodic memory impairments on classic word-list and story learning tasks from the premanifest stage of the disease, whereas semantic memory (based on letter and category fluency tasks) is considered relatively intact. Although episodic memory impairments were once considered to be executively driven (often referred to as a retrieval deficit), deficits in both recall and recognition have now been identified in the late premanifest stage of HD. Verbal episodic memory impairments in HD are subtle further away from diagnosis (e.g., 9-15 years), but remain detectable with adequate sample sizes (Stout et al., 2011).

1.2.3 Remote memory. The integrity of remote memories, such as those formed in childhood or the teenage epochs, have received relatively little empirical investigation in HD, particularly compared to the volume of studies that have examined new learning and retrieval using word-list or story tasks. Examining remote memory provides information about retrieval of memories that have already been encoded and stored rather than requiring a new learning component. This has important implications in HD because we know that encoding new information relies heavily on working memory processes and executive function (Baddeley, 2000), both of which are impaired in HD (Dumas et al., 2013), and this new-learning (encoding) requirement is absent in remote memory as target memories have already been encoded and stored. Much of the research into remote memory in HD has been assessed using the remote assessment battery, initially developed by Albert, Butters and Levin (1979). The remote assessment battery involves recognising famous faces popular in a specific

decade of time and identifying public events that occurred in a specific decade. A potential limitation of using this measure to assess remote memories is that it relies on the core principle that people 'learned' the information in a specific decade, where in practice, someone may have first learned a famous face or about an important public event much later in their lives (or earlier in the case of a 'famous face'). Despite this limitation, this battery has still allowed us to develop an initial understanding of the integrity of memories encoded from remote life epochs.

Early studies suggested that remote memory loss in people diagnosed with manifest HD was detectable when no additional cues were given to aid recall (i.e., suggesting a retrieval deficit), and that both recently diagnosed and more advanced manifest HD exhibited equivalent memory loss across time periods (Albert, Butters, & Brandt, 1981). Beatty, Salmon, Butters, Heindel and Granholm (1988) found a similar pattern of results when comparing remote memory in HD to Alzheimer's disease, noting that impairments in HD were present across all time periods (from remote to recent periods) for both unaided recall and cued recall, but to a less severe degree than people with Alzheimer's disease. The most recent study of remote memory in HD, to our knowledge, was conducted by Sadek et al. (2004), who compared remote memory in manifest HD to human immunodeficiency virus (HIV) associated dementia and Alzheimer's disease, again using an updated version of Albert and colleagues remote assessment battery from 1979. As per standard procedure, participants were required to recall the names of famous faces from different decades and identify public events. A similar pattern of findings to those yielded by the before-mentioned studies was again revealed in the HD group, who in turn performed similarly to the HIV-associated dementia participants.

Summary. Experiments examining remote memories in manifest HD have all utilised a similar testing protocol (i.e., Albert and colleagues (1979) remote assessment battery). A

relatively flat profile of impairment has been detected from these studies, with retrieval of both remote and recent memories showing similar impairments, suggesting that a temporal gradient (representing intact recent, but impaired remote memory) is *not* present in HD. There are several assumptions associated with the assessment battery used in these studies that are inherent limitations, including assuming participants are familiar with the events and faces presented to them, and assuming (if they are familiar with this information) that it was learned in a certain time epoch or period. No published research, to our knowledge, has investigated remote memory in premanifest HD, and thus more investigation is warranted to categorise remote memory in both premanifest and manifest HD.

1.2.4 Neural underpinnings of episodic memory dysfunction in HD.

Understanding the neural underpinnings of cognitive dysfunction in neurodegenerative disorders can assist in identifying biomarkers for disease progression and help to better understand neural systems underpinning cognition more broadly. Despite the number of studies examining episodic function in HD from a behavioural perspective, studies utilising neuroimaging in-conjunction with cognitive testing are relatively limited.

Studies in premanifest HD have found subtle relationships between striatal volumes and verbal learning and memory performance (Campodonico et al., 1998; Harrington et al., 2014; Solomon et al., 2007). Similar findings have been reported in manifest HD (Starkstein et al., 1992). This relationship between striatal degeneration and impaired episodic memory is typically explained in these studies as atrophy disrupting fronto-striatal circuits necessary for memory function (Solomon et al., 2007). More recent work outside the HD literature, including a review by Scimeca and Badre (2012) on striatal contributions to memory retrieval, contends that the striatum is involved with executive aspects of memory, specifically cognitive control. Furthermore, there is a growing body of research in healthy ageing that has demonstrated the important role of the striatum working in cooperation with

the hippocampus to facilitate episodic memory functioning (Sadeh, Shohamy, Levy, Reggev, & Maril, 2011). Although not the focus of this thesis and thus not examined in detail here, it should be noted that there is a substantial body of research that has investigated the neural underpinnings of working memory (i.e., the ability to hold and manipulate information in the mind for a short period of time) in HD, which has indicated consistent links between working memory and both prefrontal and striatal volume (Wolf, Vasic, Schönfeldt-Lecuona, Ecker, & Landwehrmeyer, 2009), as well as functional activity (Poudel et al., 2015) in both premanifest and manifest HD.

Summary. There have been relatively few studies of episodic memory that have compared performance on cognitive behavioural tasks to neuroimaging measures. Of the few studies that have investigated the relationship between episodic memory and brain structure, most report correlations between striatal degeneration and poorer episodic memory (as quantified by classic laboratory tasks of episodic memory). After reviewing the memory literature in HD, we assert that investigation into the neural correlates of episodic memory in HD, in a similar way that working memory has been investigated, will not only assist in understanding the cognitive profile of memory impairment in HD, but also provide advanced understanding about the neural substrates of explicit memory processes which would be a valuable contribution more broadly to the memory field.

1.3 Autobiographical Memory

Our current understanding of memory in HD has advanced our understanding of the cognitive phenotype of both premanifest and manifest HD. One aforementioned limitation of previous work is the lack of ecological relevance of measures used to quantify memory performance. While the ability to learn and retrieve word-lists in a laboratory gives us valuable information about general cognitive functioning in HD, it does not directly translate to the way people use memory in a meaningful, day-to-day capacity. Further, research

suggests that the neural correlates of episodic memory during word-list learning tasks differs from the neural correlates of autobiographical memory (Gilboa, 2004).

The focus of this thesis, autobiographical memory, is a type of ecologically relevant memory, which we investigated in order to fill this translational gap between our laboratory knowledge about how memory works in HD and how we use memory in our everyday lives. This type of memory function is crucial to understand in neurodegenerative disorders due to the relationship between autobiographical memory function and a person's sense of self, social functioning, and the ability to make decisions about the future (Bluck, Alea, Habermas, & Rubin, 2005)

Autobiographical memory is our memory for events, incidents and personal facts that have occurred over a person's lifetime. Autobiographical memories amassed across the lifespan have immense personal significance including providing us with a coherent narrative of our lives that contributes to our sense of self and personal identity over time (Conway & Pleydell-Pearce, 2000). Further, retrieving autobiographical memories enables us to bond socially with others over shared memories, and facilitates the ability to plan for the future based on our past (Alea & Bluck, 2003). Due to the profound significance of autobiographical memory for the human experience, this memory system has been studied from many different psychological perspectives (Conway & Pleydell-Pearce, 2000).

Cognitive psychology is one such psychological discipline that has endeavoured to understand the quantity and quality of information people can remember about their lives. The episodic-semantic distinction of memory first proposed by Tulving (1972) is typically utilised to understand autobiographical memory retrieval. Episodic autobiographical memories include personally-experienced event details from a specific time and place that evoke a sense of familiarity when retrieved. Retrieval of episodic autobiographical information is required for rich, high-fidelity representation of personally experienced events

(Conway, 2001). Beyond simply being able to recall event details associated with an autobiographical memory, when autobiographical memory is functioning optimally, other information that increases the feelings of re-experiencing an event or incident can be retrieved, including the spatiotemporal context in which the memory occurred, emotions and thoughts associated with the memory, and perceptual information from the landscape where the memory occurred (Levine et al., 2002). Remembering our driver's license test is a commonly recalled example of an episodic autobiographical memory. When thinking back to this event we may be able to recall an abundance of details, including where we were, the route we drove, who our instructor was, what they looked like, and how we felt on the day. Autobiographical memories also contain general conceptual knowledge or semantic information, that provide a coherent sense of self, identity and personal knowledge over time (Levine et al., 2002), for example 'I lived in Melbourne when I took my driver's license test'. A key role has been proposed for semantic autobiographical memories in supporting a sense of self-continuity and identity over time (Prebble et al., 2013).

Summary. Autobiographical memory is an ecologically relevant form of memory that facilitates retrieval of personally-experienced event details (episodic information) and personal knowledge (semantic information) from across the lifespan. Together, episodic and semantic autobiographical memories work in co-operation to facilitate the mental experiencing of reliving a personally experienced event when reminiscing on the past.

1.3.1 Neurocircuitry of autobiographical memory. Autobiographical memory retrieval involves a complex set of cognitive operations including engaging with episodic memory, self-reflection, visual imagery, emotion, executive functions and semantic processes (Svoboda, McKinnon, & Levine, 2006). Research has identified a multifaceted network of structures that appear to be activated when episodic autobiographical memories are being retrieved. Functional neuroimaging studies in healthy individuals identify a distributed

network implicated in successful autobiographical recall. It is typically accepted that the core autobiographical memory network includes prefrontal regions, medial temporal regions (including the hippocampus), and posterior parietal regions (Cabeza & St Jacques, 2007; Svoboda et al., 2006). In addition, secondary and tertiary regions are also described in the literature, including the amygdala and thalamus (Cabeza & St Jacques, 2007; Svoboda et al., 2006).

The prefrontal cortex has been implicated in numerous functions related to autobiographical memory retrieval, including reconstructive mnemonic processes, strategic retrieval, memory search, and self-referential processes (Svoboda et al., 2006). Specifically, activity in the ventrolateral prefrontal cortex has been associated with strategic retrieval and verification of information (including extracting the "gist" from episodic memories) (Fletcher & Henson, 2001; Moscovitch, Cabeza, Winocur, & Nadel, 2016; Svoboda et al., 2006; Winocur & Moscovitch, 2011). The medial frontal regions have been further associated with self-referential processes of autobiographical memory (Addis, Moscovitch, Crawley, & McAndrews, 2004; Levine, 2004).

Whereas there is agreement in the literature that autobiographical memories depend on hippocampal regions during initial encoding of information (Scoville & Milner, 1957), the role of the hippocampus in supporting retrieval of both recent and remote autobiographical memories has been debated throughout the literature. The standard model of consolidation argues that autobiographical memories (and indeed explicit memories more broadly) become less dependent on the hippocampus over time (Scoville & Milner, 1957), whereas multiple trace theory suggests that the hippocampus remains crucial for retrieval of rich autobiographical memories regardless of the remoteness of a memory (Nadel & Moscovitch, 1997). Some neuroimaging studies have supported a temporally limited role of the hippocampus for autobiographical memory retrieval, finding activation in the hippocampus

for recent, but not remote autobiographical memories (Niki & Luo, 2002; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003). Aside from these findings, there is a larger body of research that detects hippocampal activation during autobiographical memory retrieval, regardless of the recency or remoteness of memories, providing support to the multiple trace theory (Addis et al., 2004; Addis & Tippett, 2004; Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Irish et al., 2014; Maguire, Henson, Mummery, & Frith, 2001; Palombo et al., 2018; Piolino et al., 2004; Ryan et al., 2001). In addition to fMRI studies, researchers have also investigated the relative relationship between hippocampal volume and autobiographical memory function. For example, Gilboa et al. (2005), detected relationships between hippocampal volume and autobiographical performance in a sample of people with probable Alzheimer's disease. Similarly, Irish et al. (2014) reported correlations between hippocampal volume (as well as medial prefrontal and frontopolar cortical regions) and retrieval of recent and remote autobiographical memory in Alzheimer's disease and fronto-temporal dementia. In healthy-adults, the hippocampus has also been shown to play a key role in elaboration (McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2013), including the ability to provide rich and exhaustive details relating to an autobiographical event.

As well as being implicated in the retrieval of autobiographical memory, the hippocampus has been implicated in facilitating the reconstruction of spatial scenes when retrieving autobiographical memories (Wheeler, Petersen, & Buckner, 2000), an important feature associated with re-experiencing during autobiographical recall. Some theorists posit that scene construction in autobiographical memory serves as a scaffold for episodic autobiographical memory recall, suggesting that spatial context is reinstated or remembered before other information (Hassabis & Maguire, 2007; Robin et al., 2015). In addition to hippocampal involvement, the temporoparietal junction has also been implicated in retrieval of the spatial context of events (Burgess, Maguire, Spiers, & O'Keefe, 2001), whereas the

precuneus, located in the posteromedial portion of the parietal lobe, has been implicated in mental imagery and elaboration of autobiographical memory (Addis, Wong, & Schacter, 2007; Spiers & Maguire, 2007).

Beyond this core brain memory network, other regions, sometimes referred to as secondary or tertiary networks, have been implicated in successful autobiographical retrieval. We discuss other brain regions that have been associated with autobiographical memory retrieval in the next section of this introductory chapter by reviewing autobiographical memory studies in neurodegenerative disease and other brain disorders.

Summary. Autobiographical memory involves complex cognitive operations that are supported by a core brain memory network encompassing medial temporal (including the hippocampus), posterior parietal, and prefrontal regions (Cabeza & St Jacques, 2007; Svoboda, McKinnon, & Levine, 2006). The hippocampus is key region important for both encoding and elaboration of autobiographical events (McCormick et al., 2013). Beyond this core brain memory network, other regions, sometimes referred to as secondary or tertiary networks, have been implicated in successful autobiographical retrieval. Research in both healthy ageing and in brain disorders continues to advance our knowledge of the complex and widely disrupted network that supports autobiographical retrieval.

1.3.2 Autobiographical memory in ageing and neurodegenerative disorders. Autobiographical memory retrieval is particularly vulnerable to disruption in cortically-based neurodegenerative disorders, including Alzheimer's disease (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012; Irish, Hornberger, et al., 2011) and frontotemporal dementia (Irish et al., 2014; Irish, Hornberger, et al., 2011; Piolino et al., 2003). Such deficits are suggested to reflect the degeneration of key nodes within the brain's core autobiographical memory network including the medial temporal lobes, medial prefrontal cortex, and posterior parietal circuitry (Irish et al., 2014; McKinnon et al., 2008). Compared

to more cortically-affected neurodegenerative diseases, autobiographical memory research in neurodegenerative disorders with considerable subcortical pathology has been much more limited, and no research to date has examined autobiographical memory in HD. Below we review findings from autobiographical memory research in various neurodegenerative diseases and other brain disorders.

Alzheimer's disease research has yielded consistent findings of deficits in episodic autobiographical memory (Benjamin, Cifelli, Garrard, Caine, & Jones, 2015; Meulenbroek, Rijpkema, Kessels, Rikkert, & Fernández, 2010) and mixed findings for the integrity of semantic autobiographical memory. Impairments in episodic autobiographical retrieval are thought to be underpinned by the brain atrophy associated with Alzheimer's disease, which causes pronounced degeneration in the medial temporal lobes including hippocampal shrinkage. Specific components of episodic autobiographical memory have been found to be impaired in Alzheimer's disease, including impaired emotional re-experiencing of past memories (Irish et al., 2011). Although many studies have demonstrated impaired semantic memory in Alzheimer's disease (Addis & Tippett, 2004; Graham & Hodges, 1997; Kopelman, Wilson, & Baddeley, 1989), more recent studies have reported a tendency for people with Alzheimer's disease to retrieve a higher quantity of semantic memories compared to controls (Meulenbroek et al., 2010). This finding of increased retrieval of semantic memories in lieu of decreased access to episodic details during autobiographical retrieval, could be indicative of a semantic compensatory mechanism in Alzheimer's disease, similar to that seen in healthy ageing (Levine et al., 2002).

Autobiographical memory studies in frontotemporal dementia have demonstrated varied findings of impairment depending on the dementia subtype, which likely reflects the differences in neuropathology associated with these subtypes. Behavioural variant frontotemporal dementia is associated with early degeneration and atrophy in the medial and

orbital prefrontal cortices (Seeley et al., 2008), which progresses to a more mixed presentation involving frontal and temporal cortices (Williams, Nestor, & Hodges, 2005). Semantic dementia, however, is characterised by anterior temporal lobe degeneration including to the hippocampus (Hodges & Patterson, 2007). In behavioural variant frontotemporal dementia, autobiographical memory has been found to be impaired in both free and probed recall across both remote and recent time epochs (Irish et al., 2011). Although autobiographical memory impairments have been found in semantic dementia, closer analysis of the integrity of recent versus remote memory reveals relatively preserved recent autobiographical memory in comparison to remote epochs. Impaired remote memory in semantic dementia is thought to represent a loss of semantic information needed to successfully access a memory trace (Irish et al., 2011; Westmacott, Leach, Freedman, & Moscovitch, 2001).

Posterior cortical atrophy, a neurodegenerative syndrome characterised by progressive atrophy in the parietal and occipital cortices, has recently been associated with a decrease in the number of rich, episodic autobiographical details that can be retrieved, and an increase in tangential and non-episodic information not related to the autobiographical event (Ahmed et al., 2018). In their study, Ahmed et al. (2018) compared autobiographical memory performance to structural neuroimaging using voxel based morphometry (VBM). They reported that deficits in episodic autobiographical dysfunction in posterior cortical atrophy was not attributable to hippocampal atrophy or dysfunction. Instead, the authors concluded that deficits were likely driven by posterior parietal atrophy (specifically in the precuneus), through a reduced capacity for visual imagery (Ahmed et al., 2018). Collectively, these findings from autobiographical memory studies in Alzheimer's disease, frontotemporal dementia and posterior cortical atrophy highlight that the pattern of neuronal degeneration

observed in these brain disorders appears to differentially impact and impinge on specific aspects of successful autobiographical retrieval.

In terms of brain disorders with more pronounced subcortical pathology, few studies have investigated links between disease pathology and autobiographical memory function. Bose, Biswas, Pal, Basu and Das (2016) investigated autobiographical memory function in vascular disease. Researchers compared performance to a sample of people with vascular dementia that included people with and without subcortical ischemic changes. The authors reported that people with vascular dementia exhibited reductions in both semantic and episodic memory. One limitation from this finding was the heterogeneity of pathological changes in the population, which varied from ischemic changes to no ischemic changes. Aside from vascular disease, there has been a limited body of research investigating autobiographical memory in Parkinson's disease. Similar to HD, the neuropathology of Parkinson's disease involves basal ganglia pathology. In addition, Parkinson's disease involves cell death in the substantia nigra and subsequent disruption to white matter pathways in the brain (Jankovic, 2008). Published autobiographical memory literature examining autobiographical memory in Parkinson's disease remains limited and includes a study by Smith, Souchay and Conway (2010) and a follow-up study published several years later (Souchay & Smith, 2013). These studies report that free-recall of autobiographical memories is reduced (Smith, Souchay, & Conway, 2010), but that performance typically improves to a level equivalent to controls when cues are provided (Souchay & Smith, 2013). No studies to date have included neuroimaging when examining autobiographical memory in Parkinson's disease.

More recently, Esopenko and Levine (2017) characterised autobiographical memory function in a sample of people who had sustained a traumatic brain injury and had focal pathology (frontal or temporal) and diffuse axonal injury. Using a robust semi-structured

autobiographical interview (Levine et al., 2002), the authors found that compared to healthy controls, severe traumatic brain injury was associated with the retrieval of fewer episodic autobiographical details and the provision of more semantic and other details. The authors examined associations between autobiographical memory performance and regional brain volumes, finding that episodic autobiographical memory was associated with smaller volumes in the temporal, parietal and prefrontal regions. Interestingly, they also found associations between autobiographical memory and frontal white matter pathways, and the anterior basal ganglia (Esopenko & Levine, 2017). This finding is particularly relevant to the current thesis, as this highlights a potential association between the striatal regions (i.e. anterior basal ganglia) and autobiographical memory function.

Summary. Autobiographical memory dysfunction is a pervasive feature of many neurodegenerative disorders, with the most evidence for dysfunction coming from studies in more cortically affected brain disorders, and mixed-evidence emerging from subcortically based brain disorders. Autobiographical memory impairments are frequently seen in more cortically-based dementias such as Alzheimer's disease and frontotemporal dementia, which is typically ascribed to associated medial temporal lobe pathology (e.g., Irish et al., 2011). Relevant to this thesis, a recent study in traumatic brain injury found that in addition to the expected associations between the core autobiographical network and autobiographical performance, associations were also detected between atrophy in the anterior basal ganglia (i.e., the striatum) and impaired autobiographical memory retrieval (Esopenko & Levine, 2017). Taken together, there has been very few studies investigating autobiographical memory in subcortically-affected brain disorders, and even fewer that have utilised neuroimaging techniques. Studying the neural correlates of autobiographical memory in HD will a) better our understanding of the memory phenotype of HD and b) increase our

understanding of the association between striatal brain regions and the ability to retrieve personally-salient memories from the past.

1.3.3 Measures of autobiographical memory. Many studies of autobiographical memory in neurodegenerative disorders and brain disorders more broadly have been limited by the measures utilised to quantify autobiographical memory function. Due to different methodological approaches used to measure autobiographical memory, there are some limitations in directly comparing findings from different studies. In this section of the thesis introduction, we discuss three of the most frequently used measures of autobiographical memory in the dementia literature: the Autobiographical Memory Interview (AMI; Kopelman et al., 1989), the Autobiographical Fluency task (Dritschel, Williams, Baddeley, & Nimmo-Smith, 1992) and the Autobiographical Interview (AI; Levine et. al, 2002).

Several techniques have been developed and are frequently utilised by clinicians and researchers to measure and quantify autobiographical memory integrity. Kopelman and colleagues (1989) proposed the AMI in the late 1980s. The AMI is a semi-structured interview that assesses semantic and episodic memory via independent questions. An example of a semantic autobiographical memory probe or question includes: 'subject's address before going to school'. An example of an episodic autobiographical memory probe or question includes: 'recall of an incident involving a relative or visitor in the last year'. The AMI is used clinically due to relatively fast administration time and simple scoring protocol (Kopelman et al., 1989).

There are several limitations associated with using the AMI to measure autobiographical memory. The first limitation is that many of the questions require the subject to have experienced a *specific event* in their lives. For example, the subject is asked to recall specific information about *when* and *where* they were married (or if there were not married, to recall the name of someone else whose marriage they attended). This holds the

assumption that the subject would have attended a wedding during this time period. The more important limitation of the AMI is that it assumes that when answering questions categorised as semantic (e.g., names of three teachers or friends from secondary school) *only* semantic information is recalled. Similarly, when asked a question categorised as episodic in nature (e.g., recall an incident from college or the first job) it assumes the subject is recalling a unique episodic memory from a specific place in time, when it is entirely possible they are recalling a combination of episodic and semantic information, or even a general semanticised memory from that time period in response to the question/prompt.

Another commonly utilised measure of autobiographical memory is the Autobiographical Fluency Task (Dritschel et al. 1992). The Autobiographical Fluency Task involves subjects recalling as many autobiographical episodes or personal facts from different life periods. The recall of events portion of the Autobiographical Fluency Task does not request specificity of detail from subjects; rather, it encourages rapid identification of an episodic event, and then the subject is encouraged to move onto another memory. As such, recall is encouraged even if only a vague recollection is able to be retrieved, with the primary 'outcome' being *quantity* of events retrieved rather than quality or specificity of memories. For the recall of names, subjects are simply asked to recall as many names as they are able to remember from a time period (Dritschel et al., 1992). Similar to the AMI, one limitation of this task is that retrieved events that are considered 'episodic' by nature of the measure, may include semanticised memories, abstracted from time or place.

In 2002, Levine et al. proposed the AI. Similar to the AMI, the AI also employs a semi-structured interview format. In contrast to the AMI, the scoring of the AI does not consider information 'semantic' or 'episodic' based on the type of question asked but assumes episodic and semantic information is enmeshed during retrieval. The AI requires participants to recall a specific event from a life epoch and then examines the subjects'

propensity to recall semantic or episodic details about the target autobiographical event. As such, the AI measures an individual's bias towards semantic or episodic details from a single narrative, thereby working from the assumption that we recall both semantic and episodic memories simultaneously when engaging in autobiographical remembering. The AI samples additional life epochs compared to the AMI (five time periods: childhood, teenage years, early adulthood, middle adulthood, last 12-months), and uses three different levels of retrieval support (free recall, general probing, and exhaustive specific probes) to examine how prompts and probes aid autobiographical memory recall. The varied levels of retrieval support in the AI is a feature that helps to compensate for deficits in detail generation in response to an open-ended question that may not necessarily indicate evidence of an amnesic memory profile (Levine et al., 2002). This type of format is particularly useful in a neurodegenerative population where verbal fluency deficits, apathy and reduced initiation may all contribute to less detailed responses to open ended questions. Another strength of the AI is the scoring protocol used. The scoring protocol of the AI is based on the assumption that when retrieving an autobiographical event or incident, within natural discourse we will retrieve both episodic, semantic and other information (repetitions, metacognitive statements, tangential information not related to the event). The text segmentation scoring protocol of the AI further allows a more in-depth examination of the type of contextual episodic details a person retrieves about an autobiographical event, including event details, spatio-temporal context, perceptual information, and emotions/thoughts (Levine et al., 2002).

The AI and the AMI are among the most popular tools for measuring autobiographical memory, but the semi-structured interview paradigm employed in these tasks is not without some limitations. First, these paradigms work from the assumption that a person's recall is veridical in nature and responses are difficult to validate. In addition, autobiographical interviews are a type of self-disclosure (Bluck, Alea, & Demiray, 2010) and

people may be reluctant to self-disclose to study personnel in a laboratory setting, which may also attenuate the quality and quantity of autobiographical memories. Despite these limitations, semi-structured interviews, and particularly the AI, remain among the most robust methods of assessing autobiographical memory function.

Summary. There are several widely-used measures of autobiographical memory and all share the inherent limitation of difficulty validating response accuracy. Despite this limitation, there are several measures used clinically and in research that have been widely used to classify and categorise autobiographical memory integrity in healthy and clinical populations. Although the AMI is a widely utilised and useful clinical assessment tool for examining autobiographical memory, it is limited by assuming information retrieved by a person is semantic or episodic based on whether a question is classified as semantic or episodic (Kopelman et al., 1989). The AI overcomes this limitation by utilising a semi-structured interview format to assess a person's natural bias towards episodic, semantic or other information when they are retrieving an episodic event from a specific life epoch. The AI further uses a fine-grained scoring protocol that allows careful examination of the types of contextual details a person populates their autobiographical narratives with including event details, spatio-temporal context, emotions and thoughts from the event, and information about the perceptual landscape whereby a memory occurred (Levine et al., 2002). After reviewing the literature, we selected the AI to use to investigate autobiographical memory function in HD.

1.4 Reminiscence

1.4.1 Functions of reminiscence. Over the past two to three decades, autobiographical memory research has shifted from the traditional approach of only asking 'what' can be remembered across the lifespan, to also asking 'why' people think and talk about the past. As described by Bluck et al. (2005, p.92): "Examining function provides a

different and potentially complementary view of the remembering individual: the organism is not simply an information processor (emphasis is on memory capacity and veridicality) but rather an organism processing information in ecological context (emphasis is on memory utility)".

The process of thinking and talking about the past has been described in both the cognitive literature (Bluck et al., 2005; Pillemer, 1992) and the psychodynamic literature (Webster, 1993, 1997). Thinking and talking about autobiographical memories (i.e., reminiscing) is conceptualised in the cognitive literature as serving three broad functions: self, social and directive (Bluck et al., 2005; Pillemer, 1992). The self-function involves retrieving autobiographical memories to maintain a sense of being the same person over time. The social-function of autobiographical memory facilitates social bonding by providing material for conversations and creates intimacy in relationships through shared experiences and knowledge of others, and the directive-function involves retrieving memories to inform and guide present and future thinking and behaviour, as well as assisting with problem solving (Bluck & Alea, 2011). There are other models used to conceptualise the functions of autobiographical reminiscence, including Webster's reminiscence model (Webster, 1993, 1997). Webster's reminiscence model proposes autobiographical reminiscence serves eight functions; problem-solving, identity, death preparation, boredom reduction, conversation, intimacy maintenance, bitterness revival, conversation and teaching/informing. Despite theoretical models differing in the quantity and labels of identified reminiscence functions, the three-functions proposed in the cognitive psychology literature (i.e., self, social and directive) are common themes between models (Harris, Rasmussen, & Berntsen, 2014).

Memory and *the self* are considered intertwined concepts, with the accumulation of memories amassed across the lifetime providing the basis of our unique identities and sense of self (Prebble et al., 2013). Both episodic and semantic components of autobiographical

memory are thought to support self-continuity over time. It has been traditionally proposed that episodic autobiographical memory contributes to a subjective sense of self by facilitating the ability to mentally time-travel and re-experience past events (Wheeler, Stuss, & Tulving, 1997). This sense of self has also been linked to the ability to make future decisions and set goals, a form of prospection (Hershfield, 2011). Semantic memory is proposed to contribute to a more objective sense of self-continuity, with personal facts and experiences meshed together by common themes, life facts, or chapters in our lives (Grilli, Wank, & Verfaellie, 2018). More recently, it has been proposed that the contribution of episodic and semantic autobiographical memory to the self is likely more complex and changes over the lifespan, particularly in the case of neurodegenerative disorders (Strikwerda-Brown, Grilli, Andrews-Hannah, & Irish, 2018). As such, research investigating how autobiographical memory function (and impairments) contribute to a person's sense of self and identity has received increased empirical interest in recent years (Strikwerda-Brown et al., 2018), yet no research to our knowledge has investigated the relationship between autobiographical memory and sense of self in HD.

The social utility of autobiographical memory has been extensively discussed throughout the literature. Autobiographical memory serves social functions by facilitating intimacy through sharing personal and shared narratives (Bluck et al., 2005). At a fundamental level, autobiographical memories provide material for conversations (Cohen & Taylor, 1998). Furthermore, autobiographical memories may also assist in empathising with others (Alea & Bluck, 2003; Cohen & Taylor, 1998). It has further been posited that social relationships can suffer as a consequence of reduced or impaired episodic memory (Robinson & Swanson, 1990), although the body of literature supporting this is somewhat limited. Current theories suggest that both episodic and semantic elements of memory are involved in communication (Hayes, Ramanan, & Irish, 2018). Although social communication is often

affected in neurodegenerative disorders, such as frontotemporal dementia or the later stages of Alzheimer's disease, research investigating the social function or utility of autobiographical memory in neurodegenerative disorders is sparse, with no research conducted in HD.

Finally, the directive function of reminiscence involves thinking about the past to plan for the future. The ability to imagine and envisage the future has been linked to both episodic and semantic autobiographical memory (Irish & Piguet, 2013; Schacter, Addis, & Buckner, 2007). These theories suggest that thinking about past events and utilising previously stored semantic knowledge (both autobiographical and non-autobiographical) serves as a crucial basis for imagining, simulating and predicting possible future events (Schacter et al., 2007). The integrity of prospective memory has been directly examined in neurodegenerative disorders, including Alzheimer's disease and frontotemporal dementia, revealing marked deficits in future thinking (Irish & Piolino, 2016). Again, no research has examined episodic future thinking in HD, nor the relationship between autobiographical memory and episodic future thinking.

Summary. Thinking and talking about autobiographical memories (i.e., reminiscing) can serve a number of core functions including: 1) maintenance of a coherent sense of self and identity over time (*self*-function); 2) facilitation of social-bonding and intimacy in relationships through shared experiences (*social*-function), and 3) guiding present and future thinking and behaviour (*directive*-function) (Bluck & Alea, 2011; Bluck, Alea, Habermas, & Rubin, 2005; Pillemer, 1992). These functions are important for quality of life and well-being. No research to date has investigated the functions of autobiographical reminiscence in HD.

1.4.2 Autobiographical reminiscence function in neurodegenerative disorders.

The self-reported function of autobiographical reminiscence has been studied in many

different clinical and healthy populations in order to ascertain how we use our autobiographical memories over time, and to identify whether varying life circumstances impinge upon why people think and talk about their lives. As thinking and talking about autobiographical memories is related to personal goals and life roles, the self-reported function of autobiographical reminiscence would be expected to change over time to adapt to life circumstances (Alea & Bluck, 2013; Bluck & Alea, 2009). With age, autobiographical reminiscing for reflective and ruminative functions decreases over time, whereas the social function remains the most frequently used function of reminiscence regardless of age (Harris et al., 2014). These findings demonstrate that social functions of memory are particularly important in everyday life, allowing us to think and talk about shared memories to foster intimacy and closeness in our relationships. The functions of autobiographical reminiscence have also been linked to well-being and social connectedness, with Waters (2014) reporting an association between positive relationships and value within a community, and reminiscing more frequently for social, self and directive purposes. Furthermore, increased 'thinking' and decreased 'talking' about the past has also been linked to high levels of depressive symptomology in younger adult populations (Grace, Dewhurst, & Anderson, 2016). Overall these studies have highlighted how different factors, such as age, mood, and general well-being appear to affect the functions of autobiographical reminiscence.

To date, there has only been one study to our knowledge that has directly investigated the self-reported *function* of autobiographical reminiscence in a neurodegenerative population. It is surprising that the functions of reminiscence have not been more widely investigated in neurodegenerative populations, due to the wide-spread use of reminiscence-based therapies and interventions in neurodegenerative populations (discussed in the following section). Further, we know that the functions of autobiographical reminiscence (i.e., why we think and talk about the past) change dynamically with various factors over the

lifetime, and due to the impact that neurodegenerative disorders have on a person's goals, life role, and well-being, this is an area that warrants further investigation. The one published study on this topic (to our knowledge) by El Haj and Antoine (2016) investigated the function of autobiographical reminiscence in 26 older adults with probable mild Alzheimer's disease. In comparison to older adult controls, the authors reported that people with Alzheimer's disease endorsed reminiscing more frequently for death preparation (i.e., coming to terms with their own mortality) and for boredom reduction (i.e., to reduce boredom in idle times, for something to do to pass the time). Reminiscing more frequently for death preparation was also associated with increased depressive symptomology in both healthy older adults and Alzheimer's disease groups (El Haj & Antoine, 2016). The authors interpreted their findings as demonstrating that people with Alzheimer's disease may be preoccupied with reminiscing for death preparation and thoughts of their own mortality as part of the disease course. No differences were observed in how frequently people with Alzheimer's disease reported reminiscing on the past for social (conversation) or self (identity) functions. El Haj and Antoine's study (2016) has not been replicated to our knowledge or extended to other neurodegenerative profiles and remains limited by relatively small sample size and questions about levels of insight or awareness people with Alzheimer's disease may have about their own condition that might confound their responses on a self-report measure. Understanding how the self-reported function and utility of autobiographical memory may change in the early stages of neurodegenerative processes, when insight remains more preserved, may provide further valuable insight into the lived experience of someone with an emerging neurodegenerative process, and how the disease changes a person's evaluation of their own memories and life narrative. Understanding reminiscence and autobiographical memory functions in HD will allow us to more comprehensively understand how people living with HD use and appraise their autobiographical memories. By including a study of reminiscence

in the thesis, we hoped to advance our understanding in this domain, and that this knowledge may be able to be applied to designing psychosocial interventions and support for people living with HD.

Summary. Research examining the functions of autobiographical reminiscence in neurodegenerative populations is sparse. One study demonstrated comparable self-reported use of autobiographical memories for *self* (identity) and *social* (conversation) functions in Alzheimer's disease and healthy controls (El Haj & Antoine, 2016). Interestingly, the Alzheimer's disease group reported using reminiscence as a means of death preparation (i.e., coming to terms with their own mortality) and boredom reduction (i.e., for something to do to pass the time) more often than controls. No research has examined the function of autobiographical memory in HD. Due to the limited number of psychosocial interventions available in HD, categorising the frequency and function that people with HD think and talk about the past may provide a better understanding as to whether reminiscence-based therapies could be appropriate in this population.

1.4.3 Reminiscence as a psychosocial intervention. Reminiscence therapy is an intervention that has been utilised in both ageing and neurodegenerative populations in an attempt to improve mood, quality of life, cognition, and communication. Broadly, reminiscence therapy involves discussion of past activities, events, and experiences in a structured setting. Prompts such as photographs, familiar music, and familiar objects are often used as part of the therapeutic approach (Woods, O'Philbin, Farrell, Spector, & Orrell, 2018). Reminiscence therapy has become an increasing popular psychosocial intervention in dementia care and later-life depression. Reminiscence therapy was deemed popular, particularly in dementia, due to the relative preservation of older, sometimes semanticised memories in neurodegenerative syndromes. As such, it has been used as a tool to aid and encourage communication in people with neurodegenerative disorders, allowing them to

speak confidently about well-rehearsed semanticised memories (O'Philbin, Woods, Farrell, Spector, & Orrell, 2018). Early studies examining the efficacy of reminiscence therapy were often limited by small sample sizes, poorly designed interventions and inconsistent findings. Meta-analyses examining these studies subsequently called for well-designed quality randomised control trials to confirm the efficacy of the therapeutic approaches (Cotelli, Manenti, & Zanetti, 2012; Huang et al., 2015). Other reviews have highlighted the variation in intervention period length and intervention frequency as clouding the ability to determine the efficacy of reminiscence therapy as an effective therapeutic intervention (Testad et al., 2014).

A 2018 meta-analysis by O'Philbin and colleagues extracted data from 16 studies finding that across these studies, individual reminiscence therapy was associated with improvements in cognition and mood, and furthermore group approaches were associated with improved communication. Improvements in quality of life were also evident in care-home settings (O'Philbin et al., 2018). In their discussion, the authors noted that although studies are beginning to report the reminiscence protocols used as part of the intervention, more detailed manuals and standardised practices are needed in order to reliably and scientifically compare the efficacy of specific intervention types, such as simple reminiscence, life review, joint reminiscence work with families and music listening reminiscence therapy approaches. Importantly, O'Philbin et al. (2018) reported that reminiscence therapy now has a credible evidence-base and can be viewed as a useful and evidence-based psychosocial intervention.

Summary. Reminiscence therapy is an intervention that has been utilised in both ageing and neurodegenerative populations in an attempt to improve mood, quality of life, cognition, and communication. Broadly, reminiscence therapy involves discussion of past activities, events, and experiences in a structured setting. Recent findings show promise for

reminiscence therapy as an efficacious psychosocial intervention (O'Philbin et al., 2018). As psychosocial interventions in HD remain limited, and due to the currently incurable nature of the disease, considering the efficacy of evidence-based interventions (including reminiscence or autobiographical memory-based interventions) warrants further investigation in HD.

1.5 Thesis Rationale, Structure and Aims

A comprehensive review of the cognitive neuroscience literature in HD and of the autobiographical memory literature independently, demonstrate a compelling case for combining these two previously distinct areas of research, and examining autobiographical memory function in HD. From a HD perspective, this will aid in our understanding of the cognitive phenotype of the disease, allow us to better understand the neural correlates of memory function, and gain an understanding for how memory operates in the real-world for someone living with HD. More broadly, characterising autobiographical memory function and its neural basis in HD will add to our knowledge of the mechanisms underlying autobiographical memory function, particularly the association between the striatum and autobiographical memory function.

Broadly, this thesis aimed to categorise autobiographical memory in premanifest and early HD from a cognitive perspective, a neural perspective, and a functional perspective. Below are the specific aims of this research, mapped onto the chapter in which they are primarily addressed:

1) First, we aimed to categorise episodic and non-episodic (i.e., semantic) autobiographical memory across life epochs in premanifest and manifest HD. Specifically, we investigated whether memory dysfunction was present in both premanifest and early manifest HD, and the pervasiveness of these deficits. This aim is addressed in **Chapter 3: Pervasive autobiographical memory impairments in Huntington's disease.**

2) Second, we sought to identify the neural correlates of free and probed autobiographical memory in HD. We specifically aimed to investigate the role of the striatum and hippocampus in autobiographical memory function using manual tracing techniques to measure volumetry. This aim is addressed in **Chapter 4: Striatal and hippocampal correlates of autobiographical memory in Huntington's disease.**
3) Finally, we aimed to determine self-reported functions (or reasons) that people with HD report using their autobiographical memories. Specifically, we investigated the frequency with which people living with HD engage in autobiographical reminiscence for self-continuity, social-bonding, and directing-behaviour. This aim is addressed in **Chapter 5: Discrete changes in the frequency and functions of autobiographical reminiscence in Huntington's disease**

CHAPTER 2: EXPANDED METHODOLOGY

In this chapter, the general methodology of this thesis is outlined, including participant recruitment, detailed protocol relating to autobiographical memory measures, imaging acquisition, and imaging analysis protocols. We do not summarise the cognitive characterisation tasks and survey measures here because they are detailed in each separate manuscript. Information in this chapter is designed to supplement the information in the experimental papers (Chapter 3, Chapter 4, and Chapter 5) and provide a more in-depth explanation and overview of the overall methodology. Particularly, this chapter allows a thorough explanation of imaging analysis protocol utilised for the manual tracing of MR images.

2.1 General Participant Recruitment Information

2.1.1 Participant recruitment. The current study involved recruitment and testing of two participant groups:

- Participants genetically confirmed to have HD.
- Healthy controls matched with the HD group on variables including age, gender, handedness, education, and estimated IQ.

Both groups were recruited and participated in the study between January 2016 and August 2017. We recruited participants genetically confirmed to have the HD CAG expansion primarily through the Stout and Experimental Neuroscience Research Unit (Stout-ENRU) participant database, a database of people who have consented to be contacted about research studies being conducted at Monash University. In addition, we recruited participants through the state-wide progressive neurological disease clinic at Calvary Health Care Bethlehem (Caulfield, Australia) and via the Huntington's Victoria website (https://www.huntingtonsvic.org.au/).

We recruited healthy controls through the Stout-ENRU participant database and via advertisements posted around the local community.

2.1.2 Screening and inclusion criteria. To be included in the HD group, participants were required to be genetically confirmed as having the huntingtin gene expansion, as demonstrated by a CAG repeat ≥ 39. All participants in the study underwent assessment of motor, functional and cognitive symptoms by a trained neurologist using the Unified Huntington's Disease Rating Scale (UHDRS). Premanifest HD gene-carriers were required to have never received a clinical diagnosis of HD, as indicated by a UHDRS Total Motor Score (TMS) diagnostic confidence level of less than four. Participants with manifest HD were classified as stage 1 or stage 2 HD (early-HD) based on UHDRS Total Functional Capacity (TFC) assessment (as indicated by a UHDRS TFC ≥ 7). *All* participants were required to be between the ages 30 and 66 years, and were excluded if they met the following criteria:

- previous head injury or neurological condition (including stroke, epilepsy, significant episode involving a loss of consciousness)
- history of/current psychosis
- current episode of major psychiatric disorder
- history of/current alcohol or drug abuse
- comorbid neurodegenerative disorder (other than HD).

Furthermore, we required participants to be fluent in English due to language demands of the autobiographical memory tasks. We also specified that participants should be eligible for an MRI based on screening criteria provided by Monash Biomedical Imaging (MBI), where scanning took place. In addition to the above exclusion criteria, healthy control participants were required to have either: a) no family history of HD; or b) be confirmed as gene negative for the HD gene expansion.

Potential participants were either invited to participate in the study via email or telephone call (if consent given to be contacted for research studies from the ENRU research database) or by responding to advertisements by contacting researchers via telephone or

email to express their interest in participating. A telephone screening was conducted for all participants, including providing participants with an explanatory statement about the study aims and procedures, as well as providing a demographic questionnaire verbally to evaluate participants' eligibility based on the inclusion/exclusion criteria. For HD participants, we also administered the UHDRS TFC during the telephone screening session to ensure inclusion criteria was met.

During recruitment, demographic information was gathered from control participants in order to match groups on age, gender, education, and estimated premorbid IQ (as measured by the National Adult Reading Test – 2nd Version; NART-2; Nelson & Willison, 1991) with HD participants. Thus, control recruitment was staggered to begin after HD recruitment.

2.2 Autobiographical Memory Measures

2.2.1 Autobiographical Interview (AI) administration and scoring protocol. We used the AI (Levine et al., 2002) to assess autobiographical memory. The AI examines retrieval of recent and remote autobiographical events from five discrete epochs across the lifespan: early childhood (up to 11 years), teenage years (11-17 years), early adulthood (18-35 years), middle adulthood (35-55), and recent period (within the last 12-months). For younger adults, the AI epochs can be modified such that middle adulthood is excluded, and participants are instead required to recall two memories from the 'early adulthood' epoch. In the case of our study, we chose to adjust the 'middle adulthood' epoch for participants under 55 years, rather than remove it completely. Specifically, we asked participants (under 55 years of age at testing) to retrieve an event that occurred after the age of 31, but not within the last 12-months to minimise overlap with the most recent period and allow us to look at continuous timeline from participants' lives.

With the exception of the middle-adult epoch modification for younger participants before mentioned, the AI was administered as per standard protocol. First, participants were

given a visual aid of the time epochs and introduced to the task with the following prompt from the AI manual: “I am going to ask you to tell me about an event from each of these time periods from your life. You can choose any events you wish”. We next gave participants information about privacy / confidentiality followed by: “…the event you choose must be one you were personally involved in, and you must have a recollection of being personally involved. Do not pick events that you heard about from others. They must be events from a specific time and place. For example, describing a 3-week vacation would not be sufficient. However, a specific incident that happened on one day during your vacation would be good. I want you to provide as much detail as you can about the event. Our interest is not so much in which events you choose, but rather how you describe them. So do not feel pressured to pick any particular event. I want you to know that I will be asking you to give some details for these events later, so be sure to only choose events that you feel comfortable discussing in detail.”

Thus, for each epoch, participants were required to provide a detailed description of a personally experienced event that occurred at a specific time and place, not lasting longer than 24 hours in duration. Consistent with the standard administration protocol, three retrieval conditions were employed, each providing increasing levels of retrieval support: *free recall*, *general probe*, and *specific probe*. The free recall and general probe conditions were administered first for each time epoch, and then we returned to each memory for specific probing to avoid influencing the content of a participants’ free recall.

During the free recall condition, participants spoke without interruption about their chosen memory. This condition began with the prompt “tell me about an event that happened at a specific time and place during the childhood period...” As needed, non-specific general probes were then provided to encourage more detailed recall and to clarify any instructions (i.e., “Is that everything you can remember about this event?”).

After event(s) were recalled from each epoch via free recall and general probe conditions, specific probes targeting five discrete detail categories were provided (event, time, place, perceptual/sensory, and emotion/thought). Specific probes were provided both verbally and via written stimuli to maximise consistency in the quality and quantity of probes provided to each participant. Specific probes pertained to time of the event, location of the event, perceptual information associated with the event, and thoughts and feelings. An example of a line of specific probing questions included: “Can you me where this event took place? The Country? State? City? Address? Part of the Building? Part of the Room?”

Specific probing aimed to exhaust recall opportunity for participants and was thought to be a particularly important aspect of the AI for HD participants due to potential neuropsychiatric barriers (i.e., apathy) associated with HD that may reduce a person’s propensity to spontaneously give extensive answers in response to a free recall prompt. Further, if autobiographical memory deficits in HD were attributable to executive failure, this structured prompting and probing should help to ameliorate executive effort and minimise the impacts of cognitive control (recalling extraneous information) on performance.

Following specific probing for each memory, participants provided ratings about the memories they recalled using a Likert scale. Specifically, participants were asked the following questions (verbally and via written prompts):

1) How clearly can you visualise this event?
2) How much did your emotional state change from before the event occurred to after it happened?
3) How personally important is the event to you now?
4) How personally important was the event to you then?
5) On average how often do you think or talk about this event?

Regarding scoring of the AI, interviews were digitally recorded, transcribed, and then scored. We used the standard scoring protocol for the AI (see Levine et al., 2002 for detailed scoring protocol). Briefly, events were segmented into a series of informational details, which were then categorised as *internal* or *external*. Internal details were defined as those pertaining directly to the main event described, including information about the event that reflected a sense of episodic re-experiencing. Internal details were assigned to one of four discrete categories: event details, spatio-temporal details (time and place details combined as per Irish et al., 2011), perceptual details, and emotion/thought details.

External details were coded as: external event details (tangential information not directly related to the episode being described), semantic details, other details (i.e., metacognitive statements), and repetitions.

All autobiographical memories were scored by the author (AMC). 15% of interviews were scored by a second rater (Paldeep Singh [PS]). PS was blind to group membership and group hypotheses. We achieved the following intraclass correlation coefficients demonstrating excellent interrater reliability: internal free recall: .99; internal probed recall: .94; external free recall: 98; external probed recall: .94.

2.2.2 Thinking About Life Scale - Revised (TALE-R). To understand the functions (or reasons) that people report using their autobiographical memories, we used the TALE-R (Bluck & Alea, 2011). The TALE-R is a brief, self-report questionnaire that examines three specific functions: maintaining a self of personhood and identify over time (self), bonding and enhancing relationships (social), and guiding current and future behaviour (directive).

The TALE-R begins with a short introduction, followed by two baseline questions:

1) In general, how often do you think back over your life?
2) In general, how often do you talk to others about what's happened in your life?

These questions are followed by 15 items used to assess the functions of autobiographical memory (self, social, directive). Participants are required to rate each question on a Likert scale ranging from 1-5 (1 = Almost Never, 2 = Seldom, 3 = Occasionally, 4 = Often, 5 = Very Often).

Each question began with the stem: "I think back over or talk about my life or certain periods of my life…", and followed by an item. Example items include: "when I am concerned about whether I am still the same type of person that I was earlier", "when I want to develop a closer relationship with someone", and "when I want to try and learn from my past mistakes". The TALE-R subscales have acceptable to good internal consistency for the self (Cronbach's $\alpha = .83$), social (Cronbach's $\alpha = .74$) and directive functions (Cronbach's $\alpha = .78$) (Bluck & Alea, 2011).

2.3 Procedure

2.3.1 General procedure. Participants were tested individually in one session at Monash Biomedical Imaging (MBI; Clayton, Australia). Participants were first provided with the study Explanatory Statement and then gave their verbal and written consent to participate in the study. The cognitive testing session took approximately two hours, followed by thirty minutes of scanning (explained further below).

Participants were fully debriefed about the purpose of the study, and were reimbursed with $60 for their time and travel. The study protocol was approved by the Monash University Human Research Ethics Committee (CF15/2780 - 2015001133) and Calvary Health Care Bethlehem Research and Ethics Committee (15121701).

2.3.2 Imaging acquisition and pre-processing. High-resolution MRI data were acquired using a Siemens 3T scanner with 32-channel head coil at MBI. As part of the neuroimaging protocol, we collected structural MRI, DTI, and resting state fMRI data. Analyses of the DTI or fMRI data are not included in this thesis.

The acquisition parameters for the T1-weighted images consisted of 192 slices, voxel size 1mm x 1mm x 1mm, 9° flip angle. For structural imaging pre-processing we used SPM12 (Penny, Friston, Ashburner, Kiebel & Nichols, 2011). T1-weighted images were bias corrected, linearly registered with six degrees of freedom to the Montreal Neurosciences Institute (MNI) 1mm nonlinear template, and resliced.

2.4 Detailed Manual Tracing Protocols

We selected key brain regions of interest (ROI) to manually trace as part of the thesis project. Specifically, the caudate and putamen were selected due to being early and pronounced markers of the early atrophy in the HD neuropathology (Vonsattel et al., 2011). Further, the hippocampus was manually traced due to its implication in episodic memory processes (Tulving, 1972). Although other ROIs were considered (such as the amygdala), due to time constraints around the thesis and the time-consuming nature of manual tracing, additional regions were not traced and included as part of this thesis project. We utilised ITK-SNAP (Yushkevich et al., 2006) to trace images, allowing images to be traced and viewed in axial, coronal, and sagittal planes simultaneously. ITK-SNAP is a free, open-source, and multi-platform software application (www.itksnap.org/pmwiki/pmwiki.php).

For striatal regions (i.e., caudate and putamen) we utilised a published protocol by Looi and colleagues (2008; 2009) in-conjunction with other resources due to approach of tracing in axial plane. Looi and colleagues reported using an axial approach to tracing in order to minimise ambiguity that can occur in this plane, specifically delineating anteriorly the merged caudate and putamen from the nucleus accumbens, and also partial volume effects obscuring the tail of the caudate nucleus (Levitt et al., 2002; Looi et al., 2008). For the hippocampus, we used a published protocol adapted by Glikmann-Johnston et al. (2015) previously used to estimate volumes in temporal lobe epilepsy. This protocol mandated that tracing be completed in the coronal plane.

Each structure was traced by a trained researcher. AMC traced the caudate and putamen, while YGJ traced 10% of these structured to ensure acceptable interrater was achieved. YGJ and ECM traced approximately 50% of the hippocampal structures each, with interrater reliability between the two researchers was conducted on approximately 10% of scans. ICC values were excellent: left caudate: .97; left putamen: .99; right caudate: .98; right putamen: .99; left hippocampus: .98; right hippocampus: .98.

2.4.1 Caudate tracing protocol. The tracing protocol for the caudate was adapted from Looi et al. (2009). We traced initially in the axial plane, beginning inferiorly and moving superiorly using Looi et al. (2009) protocol and consulting a neuroanatomy atlas to define borders (Haines, 2004). We also consulted a tracing protocol developed by Westmoreland and Crestinger . As such, the following protocol was developed and utilised for this study:

We began tracing when the head of the caudate was distinct, which usually occurs when the white matter of the internal capsule separates the caudate head clearly from the putamen. Usually the anterior commissure separating the caudate head from the fornix, and also the posterior commissure are visible, but we began in the section where the caudate head separates from internal capsule. Because the delineation of the caudate from the putamen and the nucleus accumbens can be ambiguous, we first traced the caudate in the axial plane, and then refined the tracing if needed in the coronal plane. Moving superiorly, previously well-defined boundaries of the caudate, putamen and the internal capsule become obscured by interconnections between the caudate and the putamen. These are striatal cell bridges, which we included in the caudate tracing when they extend visibility from structure on MRI (adapted from Westmoreland & Crestinger, n.d.).

The caudate was thus outlined by drawing a line along the medial border of the internal capsule, around the head of the caudate and along the lateral wall of the lateral

ventricle, inferiorly to superiorly, on an average of 20–25 slices. The cortex adjacent to the interhemispheric fissure is excluded. Small blood vessels representing cribriform change are included in the ROI. The small section of the lateral ventricle that indents the caudate head is excluded. We included the section of the caudate head that curves along the lateral ventricle, but not the tissue inside the volume of the ventricle, which is choroid plexus. We traced the tail of the caudate in the superior slices, noting that this can be somewhat indistinct, but extends along the wall of the lateral ventricle. In particular, we traced the most distinct border of the lateral ventricle, which is not necessarily on the edge of the ventricles due to partial volume effects. We distinguished caudate from the corona radiata, which is a more laterally located grey/white striated band in the middle of the white matter projections of the internal/external capsule. The last slice was defined as when the caudate can last be seen distinct from the wall of the lateral ventricle superiorly. Consistent with Looi et al. (2008), when ambiguity arose, we preferenced tracing distinct boundaries over arbitrary rules, in order to achieve reliability. At the end of the tracing, we rechecked the entire image in the coronal plane referencing neuroanatomy atlas (Haines, 2004). After fixing any errors or inconsistencies in the coronal plane, images were checked for consistency in the sagittal plane.

2.4.2 Putamen tracing protocol. When tracing the putamen, we utilised a tracing protocol developed by Looi and colleagues (2009) again, in conjunction with Westmoreland and Crestinger (n.d.) and consulting a neuroanatomy atlas to define borders (Haines, 2004). Again, we traced primarily in the axial plane:

For the inferior boundary, we selected the first section in which the putamen is distinct from the head of the caudate, separated by the white matter of the internal capsule and separated from the globus pallidus by a thin lamina of white matter. Reference images for representative sections were used, including the point of differentiation from the nucleus

accumbens and caudate. The anterior boundary was defined by separation from the caudate head by the anterior limb of the internal capsule. The lateral border of the putamen was traced by following the margin along the white matter of the external capsule. Small blood vessels representing cribriform change were included in the region of interest. Striatal bridges are considered part of the caudate when ambiguous, but these often move between structures as you move superiorly, and in these cases they can be included in the putamen when clearly detached from caudate. The medial border of the putamen was traced along the anterior limb of the internal capsule and then following the margin along the lamina of white matter separating it from the globus pallidus through to the genu of the internal capsule. In tracing this medial border, we used the most distinct boundary between the body of the putamen and the lamina of white matter separating it from the globus pallidus. The superior boundary was the last section in which the putamen was visible. We used symmetry of the right and left hemispheres to judge where the outline should be traced. Consistent with the caudate, the entire image was first checked in the coronal plane and then in the sagittal plane, referencing neuroanatomy atlas (Haines, 2004).

2.4.3 Hippocampus tracing protocol. We utilised a protocol established by (Watson et al., 1992) and adapted by Glikmann-Johnston et al. (2015) to manually trace the hippocampi. The following protocol excerpt explains key neuroanatomical markers involved in tracing the hippocampus (Glikmann-Johnston et al., 2015, p.564):

"At its anterior part, the alveus was used to distinguish the hippocampus from the amygdala. If the alveus was not visible, the inferior horn of the lateral ventricle was used as a marker to separate the hippocampal head from the amygdala. A horizontal line was drawn connecting the plane of the inferior horn of the lateral ventricle with the surface of the uncus. The inferior margin of the hippocampus was outlined to include the subicular complex and the uncal cleft with the border separating the subicular complex from the parahippocampal

gyrus being defined as the angle formed by the most medial extent of those two structures. Measurements in the hippocampal body and tail included the subicular complex, hippocampus proper, dentate gyrus, alveus, and fimbria. In the hippocampal tail, the crus of the fornix, isthmus of the cingulate gyrus, and parahippocampal gyrus were excluded. The posterior border of the hippocampus was defined as the coronal slice in which the fornix clearly separated from the hippocampus and its fimbria."

CHAPTER 3: MANUSCRIPT ONE – PERVASIVE AUTOBIOGRAPHICAL MEMORY IMPAIRMENTS IN HUNTINGTON'S DISEASE

3.1 Explanatory Notes for Manuscript One

Manuscript One aimed to categorise autobiographical memory across life epochs in late premanifest and manifest HD. There has been limited research investigating remote memory in manifest HD, and no published research to date investigating remote memory in premanifest HD. Furthermore, no published research to date has investigated autobiographical memory (remote *or* recent) in people with HD CAG expansion. As such, we draw on literature from non-autobiographical memory studies in HD, as well as autobiographical memory studies from other neurodegeneration populations in the introduction of this paper, as we did when developing the aims and hypotheses.

We utilised the Autobiographical Interview (AI; Levine et al., 2002) for this task due the large volume of cognitive data gained from this measure, as a result of the fine-grained scoring protocol employed. This method was laborious in-nature, requiring extensive interviewing, transcribing and coding. This paper addressed the first broad aim of this thesis: to investigate autobiographical memory in HD from a cognitive perspective, by determining 'what' people living with HD could remember across their life.

We have kept the formatting of this chapter consistent with the remainder of the thesis. As this chapter has been published in *Neuropsychologia*, we have included a copy of the published article in Appendix A.

Pervasive Autobiographical Memory Impairments in Huntington's Disease

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Abstract

Autobiographical memory dysfunction is a pervasive feature of neurodegenerative disorders, but less is known about the integrity of autobiographical memory in Huntington's disease (HD). Deficits in anterograde verbal episodic memory on traditional neuropsychological tests have been detected in HD, however, whether personally-relevant autobiographical retrieval is also affected is unknown. We examined autobiographical memory performance in 26 participants genetically confirmed to have HD who were in the peri-manifest stage of the disease (including 12 in the late premanifest stage and 14 who were early diagnosed), and 24 matched controls using the Autobiographical Interview (AI), a semi-structured interview assessing retrieval of autobiographical details from discrete epochs across the lifetime. Relative to controls, people with HD exhibited global episodic autobiographical memory impairments, regardless of recency or remoteness of the memory being retrieved. While specific cues bolstered the retrieval of episodic (internal) details in HD participants, their performance remained significantly below that of controls. Moreover, following probing, people with HD retrieved more extraneous (external) details not directly related to the autobiographical event they originally retrieved, including semantic details, repetitions, and metacognitive statements. Our results reveal marked autobiographical memory dysfunction in HD, not directly attributable to strategic retrieval deficits, and suggest that autobiographical memory impairment may represent an overlooked feature of the cognitive phenotype of HD.

Keywords: episodic memory, semantic memory, dementia, hippocampus, striatum.

Huntington's disease (HD) is an inherited neurodegenerative disorder characterised by progressive cognitive, neuropsychiatric and motor symptoms. The unequivocal presence of the characteristic motor signs of HD (e.g., chorea) defines the current diagnostic basis for when HD is considered manifest; however, cognitive decline is detectable at least ten years prior to this diagnostic threshold (Paulsen et al., 2008). Deterioration of executive function, emotion recognition, and anterograde episodic memory are among the known early cognitive deficits in HD, and are detectable in the years leading up to, as well as after diagnosis (Coppen, van der Grond, Hart, Lakke, & Roos, 2018; Kordsachia, Labuschagne, & Stout, 2017; Stout et al., 2011).

Episodic memory dysfunction has been documented on standard neuropsychological tests of story and word-list recall in both premanifest and diagnosed HD (Montoya et al., 2006; Solomon et al., 2007). Impairments in semantic memory (facts and knowledge) have also been reported in HD, however, these difficulties are typically attributed to initiation and retrieval dysfunction, rather than a breakdown in semantic knowledge stores *per se*, which remain relatively preserved (Hodges, Salmon, & Butters, 1990; Rosser & Hodges, 1994). Limited research has endeavoured to investigate whether there is a differential impairment in recent or remote memory in HD. The few published studies in this area have used testing protocols primarily taxing semantic memory via public event questionnaires (e.g. well-known events that occurred in different decades) or famous face recognition tasks (faces of public figures who were famous in different decades). These studies reveal disruption of non-personal remote and recent memory in people with HD (Albert, Butters, & Brandt, 1981; Beatty, Salmon, Butters, Heindel, & Granholm, 1988). In contrast, the status of personally-relevant recent and remote memories remains unclear as no study to date has investigated the integrity of autobiographical memory in HD.

Autobiographical memory is our memory for personally experienced events and personal knowledge amassed across the lifespan (Conway, Singer, & Tagini, 2004), and involves both episodic and semantic components (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). The capacity to remember information about one's own life is linked to both wellbeing and sense of identity (Addis & Tippett, 2004; Jetten, Haslam, Pugliese, Tonks, & Haslam, 2010; Prebble, Addis, & Tippett, 2013). Episodic autobiographical memories are recollections of personally experienced events and occurrences from a specific time and place from our lives that leave robust memory traces over time (Moscovitch, Cabeza, Winocur, & Nadel, 2016). Such memories create a feeling of re-experiencing when recollected and include perceptual information, spatiotemporal context, and emotional content (Irish, Hornberger, et al., 2011; Levine et al., 2002). Mounting evidence reveals that enmeshed within the autobiographical narrative are semantic elements, comprising extended events, personal facts and knowledge from our lives (Strikwerda-Brown, Mothakunnel, Hodges, Piguet, & Irish, 2018). Previous studies have documented a shift from episodic to semantic styles of retrieval with increasing age, with older adults displaying reduced episodic details, offset by an increase in semantic information (Levine et al., 2002), a process that likely serves important adaptive functions.

Autobiographical memory retrieval is particularly vulnerable to disruption in neurodegenerative disorders, including Alzheimer's disease (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012; Irish, Hornberger, et al., 2011) and frontotemporal dementia (Irish et al., 2014; Irish, Hornberger, et al., 2011; Piolino et al., 2003). Such deficits reflect the widespread degeneration of key nodes within the brain's core memory network including the medial temporal lobes, medial prefrontal cortex, and posterior parietal circuitry (Irish et al., 2014; McKinnon et al., 2008). Compared to more cortically-affected neurodegenerative diseases, autobiographical memory research in neurodegenerative

disorders with considerable subcortical pathology has been limited. The few studies in Parkinson's disease have found that free-recall of autobiographical memories is reduced (Smith, Souchay, & Conway, 2010), but that performance improves to a level equivalent to controls when cues are provided (Souchay & Smith, 2013). HD is characterised by striking disruption to fronto-striatal circuitry and pronounced striatal atrophy detectable up to 20 years before clinical diagnosis (Tabrizi et al., 2013), which progresses to more widespread global atrophy to both grey and white matter (Vonsattel, Keller, & Ramirez, 2011), including hippocampal atrophy (Douaud et al., 2006; Rosas et al., 2003; van den Bogaard et al., 2011). Evidence regarding hippocampal integrity in premanifest HD has been mixed, with some studies detecting no differences between premanifest HD and controls (Possin et al., 2017), while others report subtle volume reductions in people with late premanifest HD (Faria et al., 2016; van den Bogaard et al., 2011).

The aim of this study was to determine whether episodic memory deficits in HD extend to the domain of personally-relevant retrieval of the past using a widely used measure of autobiographical memory, the Autobiographical Interview (AI; Levine et al., 2002). We further examined whether autobiographical memory impairments in HD affect recent and remote memory recall comparably, and whether impairments manifest in a graded manner across time periods. In addition, we sought to establish how the retrieval of specific types of contextual details is altered in HD using a fine-grained scoring method. Finally, to understand the potential mechanisms driving autobiographical memory impairments in HD, we examined the relationship between autobiographical memory and traditional neuropsychological tasks. Based on known episodic memory deficits in HD from previous studies, we predicted that people with the huntingtin gene expansion, regardless of whether they were in the early manifest or late premanifest phase, would exhibit impaired episodic

autobiographical memory retrieval compared to healthy age-matched control participants, with autobiographical memory ability varying in relation to the severity of HD.

Methods

Participants

We recruited 26 participants genetically confirmed to have the HD gene in the peri-manifest stage of the disease, including 14 participants with early stage [or manifest] HD and 12 participants who were estimated to be at the late premanifest stage of HD. Premanifest HD participants in our sample were estimated, based on their ages and CAG repeat expansion sizes, to be within 10 years to clinical diagnosis with an estimated average years to diagnosis of 3.42 years as per Langbehn and colleagues (2010) formula, and had a Disease Burden Score (DBS) > 250 (DBS formula: (CAG repeat length – 35.5)*age; Penney, Vonsattel, Macdonald, Gusella & Myers, 1997). Further, all HD participants had a Total Functional Capacity ≥ 7 (Huntington Study Group, 1996), suggesting minimal to moderate clinical impairments in the overall HD sample. For characterisation of disease progression, all participants with HD were evaluated using the motor and functional components of the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996). A higher UHDRS Total Motor Score indicates more severe motor signs, while higher scores on the UHDRS Total Functional Capacity scale indicate less functional impairment on basic activities of daily living.

As expected, premanifest HD participants in our sample had significantly lower UHDRS Total Motor Scores compared to manifest HD participants (p <.001; premanifest HD: M = 1.17, SD = 2.37; manifest HD: M = 17.31, SD = 10.04) and had a significantly higher UHDRS total functional capacity (p <.001; premanifest: M = 12.83, SD = .39; manifest: M = 10.14, SD = 2.14). The HD subgroups did not differ significantly in terms of

their DBS, suggesting comparative estimated disease burden between groups (p = .24; premanifest: M = 321.96, SD = 53.87; manifest: M = 348.86, SD = 58.87).

For comparison, we recruited 24 healthy control participants matched to the overall HD cohort of participants for age, sex, and estimated premorbid intelligence. For recruitment, we identified participants from the Statewide Progressive Neurological Disease Service at Calvary Health Care Bethlehem and from our internal research volunteer database at Monash University (Clayton, Australia). Exclusion criteria for HD participants included a diagnosis of a neurological disorder other than HD, diagnosis of a severe psychiatric condition, alcohol and other drug abuse, and limited English proficiency (because of language demands of the autobiographical memory task). The same exclusion criteria applied to control participants, with additional inclusion criteria of having no family history of HD or confirmation as gene-negative.

Ethical approval was obtained from the Monash University Human Research Ethics Committee and Calvary Health Care Bethlehem Research Ethics Committee, and written informed consent was obtained from each participant. Reimbursement was offered to cover travel costs and time for all participants.

Cognitive Characterisation

To estimate intellectual ability and cognition, we used traditional neuropsychological tests of episodic memory, verbal (phonemic) fluency, and visuomotor search and attention. Estimated premorbid intellectual functioning was assessed using the National Adult Reading Test 2nd Edition (NART-2; Nelson & Willison, 1991), which requires participants to read aloud from a list of words for which correct pronunciation differs from reading based only on phonetics. We administered the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996), which is a 15-item word-list learning task, to characterise verbal anterograde encoding and retrieval, enabling us to index our sample to previous HD memory studies, which have

typically employed word-list learning tasks. For phonemic fluency, we asked participants to generate words beginning with a particular letter for one minute each (F, A, S; Strauss, Sherman & Spreen, 2006). The Trail Making Test (TMT; Reitan, 1958) was used to assess divided attention. The Symbol Digit Modalities Test (SDMT; Smith, 1982) was included as the most sensitive paper and pencil test for HD, enabling us to compare cognitive impairment severity across studies. Finally, we administered the Centre for Epidemiological Studies Depression Scale Revised (CESD-R; Eaton, Smith, Ybarra & Muntaner, 2004), as depression occurs frequently in HD and is associated with memory impairment (Williams et al., 2007). Select cognitive and demographic information for all participants is detailed in Table 1.

Table 1

Demographic Information and Cognitive Characterisation for all Participants. Mean ± Standard Deviation (Range).

	Premanifest HD	Manifest HD	Control	*p*-value	Significant group differences
Sex (F:M)	8:4	4:10	12:12	-	
Age in Years	47.25 ± 6.92 (39-56)	54.71 ± 7.61 (43-66)	50.17 ± 7.56 (39-65)	.042*	Manifest HD > Premanifest HD
Estimated FSIQ	107.66 ± 8.04 (97-126)	108.10 ± 9.33 (95-123)	110.14 ± 9.78 (91-127)	.69	-
CESD-R	4.83 ± 5.22 (0-16)	7.86. ± 9.40 (0-29)	8.46 ± 9.38 (0-37)	.48	-
RAVLT Delay	9.33 ± 3.60 (2-15)	7.57 ± 2.98 (3-12)	12.17 ± 2.12 (8-15)	<.001*	Control > Premanifest HD, Control > Manifest HD
SDMT	50.42 ± 13.09 (34-78)	36.64 ± 10.00 (18-51)	59.42 ± 8.64 (39-72)	<.001*	Control > Premanifest HD > Manifest HD
Verbal Fluency	42.08 ± 11.13 (29-60)	41.86 ± 15.17 (17-63)	50.58 ± 9.95 (37-77)	<.001*	Control > Premanifest HD, Control > Manifest HD
TMT (B-A)^	32.10 ± 22.54 (14-88)	44.15 ± 50.59 (-5-173)	-	.49	-

Note:* = p <.05. P-value based on univariate analysis of variance. Significant group differences denote significant post-hoc tests between groups. ^ TMT data only available for HD participants. Abbreviations: HD = Huntington's disease; FSIQ = full scale intelligence quotient; RAVLT = Rey Auditory Verbal Learning Test; SDMT = Symbol Digit Modalities Test; TMT (B-A) = Trail Making Test (Part B minus Part A); CESD-R = Center for Epidemiologic Studies Depression Scale-Revised

Autobiographical Memory Assessment

The Autobiographical Interview (AI; Levine et al., 2002) is a widely used measure of autobiographical memory performance that examines retrieval of recent and remote autobiographical events from five discrete epochs across the lifespan: early childhood (up to 11 years), teenage years (11-17 years), early adulthood (18-30 years), middle adulthood (31-55), and recent period (within the last 12-months). For each epoch, participants are required to provide a detailed description of a personally experienced event that occurred at a specific time and place, not lasting longer than 24 hours in duration. For our sample, the 'middle adulthood' epoch was modified for participants under 55 years of age, whereby they were asked to retrieve an event that occurred from the age of 31 onwards, but *not within* the last 12-months to minimise overlap with the most recent period.

Consistent with the standard administration protocol, three retrieval conditions were employed, each providing increasing levels of retrieval support: *free recall*, *general probe*, and *specific probe*. During the *free recall* condition, participants spoke without interruption about their chosen memory. As needed, non-specific *general probes* were then provided to encourage more detailed recall and to clarify any instructions (e.g., "Is that everything you can remember about this event?"). After event(s) were recalled from each epoch via free recall and general probe conditions, *specific probes* targeting five discrete detail categories were provided (event, time, place, perceptual/sensory, and emotion/thought). Specific probes were provided both verbally and via written stimuli, to maximise consistency in the quality and quantity of probes provided to each participant.

Interviews were digitally recorded, then transcribed, and scored. We used the standard scoring protocol for the AI (see Levine et al., 2002). Briefly, events were segmented into a series of informational details, which were then categorised as *internal* or *external*. Internal details were defined as those pertaining directly to the main event described, including

information about the event that reflected a sense of episodic re-experiencing. Internal details were assigned to one of four discrete categories: event details, spatiotemporal details (time and place details combined), perceptual details, and emotion/thought details. External details were coded as: external event details (tangential information not directly related to the episode being described), semantic details, other details (i.e., metacognitive statements), and repetitions.

In keeping with the original scoring protocol, we combined free recall and general probing scores, hereafter referred to as '*free recall'*, while the total of free recall, general probe, and probed recall conditions created the *'probed recall'* composite score. AMC scored all autobiographical interviews, with 15 of these interviews randomly selected and scored by a second rater (PS) who was blind to study hypotheses and group membership, achieving the following intraclass correlation coefficients: internal free recall: .99, internal probed recall: .94, external free recall: .98, external probed recall: .94. A scored, deidentified interview sample is provided in Supplementary Materials.

Procedure

Participants attended a single session for testing by an examiner (AMC), which took approximately 90 minutes. Testing included measures for characterisation of cognitive functioning, as well as autobiographical memory.

Statistical Analysis

Data were analysed using SPSS Version 23. Variables were assessed for normality using Kolmogorov-Smirnov tests. For our first analysis, profiles of autobiographical memory retrieval across epochs were examined using a 3 x 2 x 5 mixed design analysis of variance (ANOVA) with planned comparisons exploring group (premanifest HD, manifest HD, controls), detail type (internal, external), and epoch (early childhood, teenage years, early adulthood, middle adulthood, and the last 12-months). This analysis was run for free and

probed conditions independently. We then conducted the same analyses (for both free and probed recall) using age as a covariate, because of age differences between groups.

The above analyses revealed no significant differences between premanifest and manifest HD participants on key variables of the AI. In subsequent analyses, we therefore combined the HD groups as one 'peri-manifest' HD group to increase study power and to minimise the potential confound of age on autobiographical retrieval. Non-parametric tests (Mann-Whitney's *U*) were used to examine group differences in the profile of contextual details retrieved by HD and control participants, given the non-normal distribution of the data. Finally, Pearson's correlations were run to explore associations between AI performance (specifically retrieval of internal details) and measures of HD progression (DBS, UHDRS Total Motor Score, UHDRS Total Functional Capacity, Years to Diagnosis), as well as select measures of cognitive function including delayed recall on the RAVLT, SDMT, and phonemic fluency. A conservative threshold of $p = .01$ was adopted to guard against Type 1 error due to multiple comparisons. Effect sizes are reported, where appropriate, using eta-squared (η_p^2).

Results

Overall Autobiographical Memory Performance

For the free recall condition of the AI, a group x detail type x epoch mixed-design ANOVA yielded a main effect of detail type ($F(1,47) = 52.32$, $p < .001$, $\eta_p^2 = .53$) with participants retrieving more internal than external details overall. A significant main effect of group was observed ($F(2,47) = 9.52$, $p < .001$, $\eta_p^2 = .29$), with planned comparisons revealing that controls recalled more details overall than both premanifest ($p = .001$) and manifest HD participants ($p = .001$), but no difference between premanifest and manifest HD groups ($p = .96$). A significant detail type x group interaction ($F(2,47) = 44.48$, $p < .001$, $\eta_p^2 = .65$) was also observed. As can be seen in Figure 1, controls retrieved more internal details than both

premanifest HD and manifest HD participants (*p*s <.001), with no difference between the HD groups ($p = .65$). None of the groups differed significantly from one another for recall of external details (all *p*s > .24). A detail type x epoch interaction approached significance ($F(4,44) = 2.42$, $p = .06$, $\eta_p^2 = .18$), however no other significant main effects or interactions including epoch were detected (*p*s > .80).

For the probed recall condition of the AI, a similar pattern of findings emerged, including a main effect of detail type ($F(1,47) = 189.48$, $p < .001$, $\eta_p^2 = .80$), with more internal details recalled overall ($p = .001$). Again, we found a main effect of group ($F(2,47) = 4.98$, $p < .01$, $\eta_p^2 = .18$) with controls retrieving more details overall than manifest HD ($p = .004$) and a trend towards controls retrieving more details than premanifest HD ($p = .05$). Again, no difference was observed in the number of details recalled by premanifest and manifest HD groups ($p = .43$). We also found a significant detail x group interaction ($F(2,47) = 40.20$, $p < .001$, $\eta_p^2 = .63$) with both HD groups retrieving fewer internal details compared to controls (*p*s < .001). Again, HD groups did not differ from one another for total internal probed recall ($p = .29$). Interestingly, when probed, premanifest HD provided significantly more external details compared to controls ($p = .02$), while a trend was detected in terms of manifest HD retrieving more external details than controls ($p = .08$). Again, we did not detect a difference between HD groups for external details following probing *(*$p = .48$; see Figure 1). No other interactions or main effects were observed (all *p*s > .42).

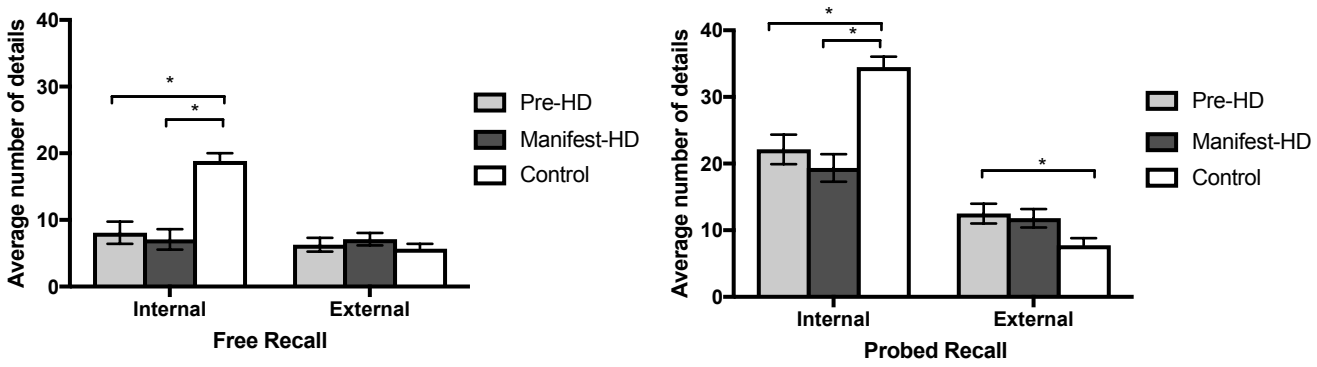

Figure 1. Internal and external details recalled by premanifest HD, manifest HD, and control participants on the Autobiographical Interview. Details are averaged across time periods for free recall and probed recall. Error bars represent standard error of the mean. Note: Pre-HD = premanifest HD. * p <.01

We conducted the same group x detail type x epoch mixed-design ANCOVA with age as a covariate for both free and probed recall, because of the significant difference in age between groups in our sample. For free recall, we detected the same pattern of findings as reported in the absence of the age covariate, with the exception of detail type, which no longer reached statistical significance ($F(1,47) = 2.64$, $p = .11$, $\eta_p^2 = .05$). For probed recall, the pattern of findings remained the same, including all main effects and interactions reported in the absence of the age covariate.

Given the comparable profile of retrieval across the main AI metrics of interest in the late premanifest and early manifest HD groups, we combined all HD participants into one 'peri-manifest' group (n = 26) to examine profiles of contextual details (reported below). This enabled us to avoid the confound of age when comparing our findings to control participants.

Profiles of Contextual Details

Looking across the internal detail subcategories, HD participants displayed global deficits relative to controls irrespective of detail type (e.g., event, spatiotemporal, perceptual, emotion/thought), across free and probed conditions (all *p*s <.001; Figure 2).

To determine whether subcategories of internal details differed within each group, we conducted a series of Wilcoxon signed-rank tests. In the free recall condition, both HD and control groups provided significantly more event details relative to all other internal detail subcategories (*p*s <.001). For free recall, HD participants also provided more spatiotemporal details compared to perceptual ($p < .001$) and emotion details ($p = .002$), with no further differences between perceptual and emotion details ($p = .66$). The control group trended towards providing more spatiotemporal details compared to emotional details ($p = .03$), however no other differences between subcategories were evident (*p*s > .25).

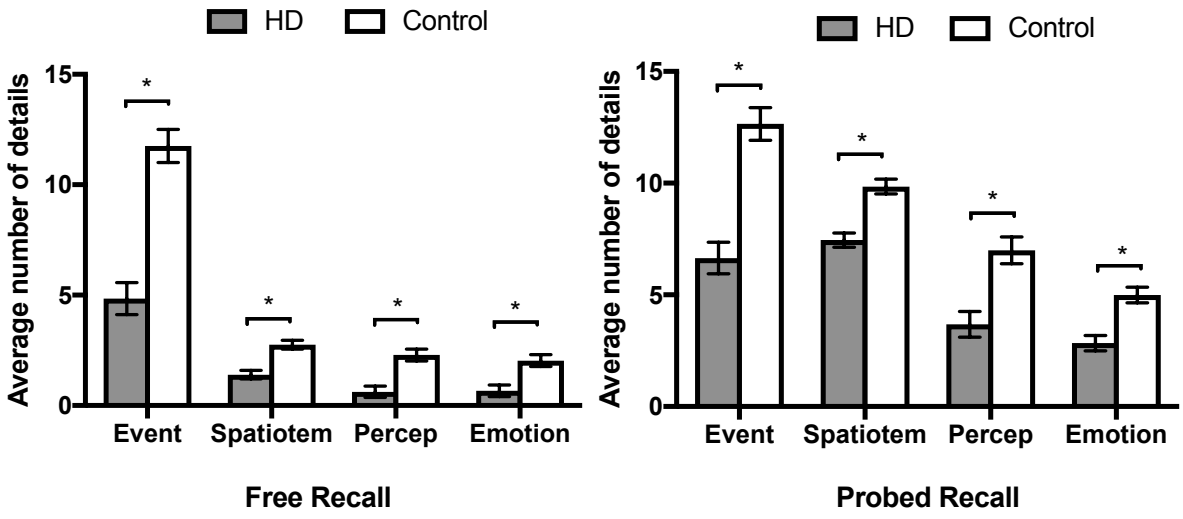

Figure 2. Breakdown of mean internal (episodic) details retrieved by perimanifest HD and control groups across free recall and probed recall. Error bars represent standard error of the mean. Spatiotem = Spatiotemporal, Percep = Perceptual, Emotion = Emotion/Thought. * *p* <.001.

For probed recall, HD participants continued to provide more event details compared to perceptual and emotional details (*p*s <.001). People with HD further provided more spatiotemporal details compared to both perceptual and emotional details (ps <.001), and more perceptual details compared to emotional details ($p = .008$).

For probed recall, the control group provided more event details compared to all other subcategories (*p*s <.001), as well as more spatiotemporal details compared to both perceptual ($p = .003$) and emotional details ($p < .001$). Finally, more probed perceptual details were recalled by controls compared to emotion details ($p = .002$).

Profiles of External Details

When comparing the subcategories of external details (e.g., external-event, repetitions, other, semantic), we found a trend towards HD participants producing more repetitions than controls ($U = 1.87$, $p = .06$), but no other significant group differences (all other *p*s >.14). Following probing, however, the HD group produced significantly more repetitions ($U = 2.87$, $p = .004$), and other details (e.g., metacognitive) ($U = 3.34$, $p = .001$) compared to controls. We also observed a trend towards the HD group producing increased semantic details relative to controls ($U = 2.53$, $p = .012$). See Figure 3.

To determine whether subcategories of external details differed within each group, we again conducted a series of Wilcoxon signed-rank tests. Within the HD group, in both free and probed recall conditions, more semantic details were provided compared to all other external subcategories (*p*s < .002). In both recall conditions, the HD group also provided more other details compared to repetitions (*ps* <.01). Further, in probed recall, HD participants provided more other details compared to external event details ($p < .001$). No further differences were detected between other external detail categories in the HD group (*p*s > .10).

Controls provided more semantic details than repetitions (p <.001) or other details (p = .001) for both free and probed recall. Across both recall conditions, trends were also observed towards more semantic compared to external-event details (free recall: p = .04, probed recall: p = .013). In the free recall condition, controls provided more other details compared to repetitions (p <.001). We did not detect any other differences between external subcategories for controls across recall conditions (ps > .10). See Supplementary Materials for raw scores (means, standard deviation) for the internal and external detail subcategories.

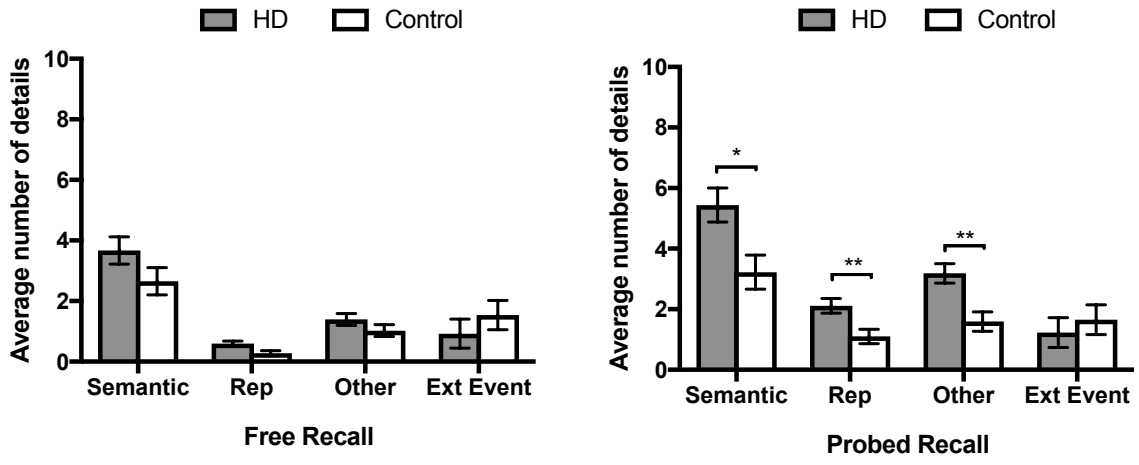

Figure 3. Breakdown of mean external details retrieved by perimanifest HD and control groups across free recall and probed recall. Error bars represent standard error of the mean. Rep = Repetition, Ext Event = External Event. * p <.05; ** p <.01.

Disease Severity and Episodic Autobiographical Memory

In relation to HD progression, the presence of more severe motor signs (UHDRS Total Motor Score) was associated with fewer total internal details in the probed recall condition (r = -.56, p = .004). Similarly, lower functional capacity (UHDRS Total Functional Capacity) was associated with poorer probed retrieval of internal details (r = .57, p = .003).

No significant association was observed between DBS and free or probed retrieval of internal details (*p*s >.70). Within the premanifest HD sample, estimated years to diagnosis (Langbehn et al., 2010) was not associated with total free (r = .30, p = .34) or probed (r = .46, p = .14) internal details.

Associations Between Autobiographical Memory Performance and Other Cognitive Domains

We found no significant associations between cognitive measures of delayed verbal recall, executive function, or phonemic fluency and free recall of internal details (all *p*s > .06). For probed recall of internal details, while no significant associations survived at the conservative threshold (p = .01), we observed a trend between retrieval of probed internal details and delayed episodic recall (r = .47, p = .015) as well as phonemic fluency (r = .47, p = .016).

Discussion

This study is the first to demonstrate that autobiographical memory dysfunction is a pervasive feature of HD, in both its late premanifest and manifest stages. This finding is consistent with previous research in dementia syndromes (Barnabe et al., 2012; Irish, Hornberger, et al., 2011; Piolino et al., 2003), and provides new evidence that autobiographical memory dysfunction is present in neurodegenerative disorders characterised by early subcortical pathology. Within the HD literature, previous research has established deficits on tasks measuring anterograde episodic memory (Montoya et al., 2006; Solomon et al., 2007; Stout et al., 2011). We extend these findings to a more ecologically valid memory domain, revealing global impairments in the retrieval of personally-relevant recent and remote memories in both late premanifest and manifest HD.

The first key finding from our study concerns the propensity for people with HD to provide significantly fewer internal (episodic) autobiographical details relative to controls,

irrespective of probing condition. Whereas specific probing (compared to free recall) yielded better recall of internal details in HD participants, even with these improvements their performance fell short of normal control levels. Interestingly, however, structured probing significantly inflated external content for premanifest HD, with a trend towards increased external details in manifest HD. Looking across both HD subgroups, these higher levels of probed (vs free) external details reflected elevated levels of repetitions and metacognitive statements, as well as a trend towards higher numbers of semantic details. Within-group comparisons revealed that semantic content dominated the external detail profile in both HD and control participants. Previous studies using the AI in dementia populations have documented compensatory increases in the provision of external details in the face of compromised retrieval of internal details (Irish, Hornberger, et al., 2011; Levine et al., 2002; McKinnon et al., 2008). Although some studies have demonstrated that this increase in external details reflects the production of off-target external-event details (Irish, Addis, Hodges, & Piguet, 2012), in the case of HD, structured probing appears to bolster repetitions and metacognitive statements, which are not typically viewed as content-rich (Strikwerda-Brown et al., 2018). The increase in external details in HD may be a manifestation of limited cognitive control, or a general inefficiency in the focused retrieval of autobiographical information. Longitudinal studies will prove particularly important in further understanding these profiles of retrieval (e.g., Irish et al., 2018).

Turning our attention to the profile of contextual details retrieved by the HD group, global deficits were observed irrespective of internal detail type (i.e., event, spatiotemporal, perceptual, emotion/thought) or probing condition (free recall, probed recall), a finding that may reflect a general impairment in autobiographical memory specificity. Similar profiles of impairment have been reported in other neurodegenerative disorders such as frontotemporal dementia, suggested to reflect an impairment in self-referential processing (Irish, Hornberger,

et al., 2011). We note that the impairment of emotion/thought details is of particular interest in HD, given the widespread disruption to emotional processing in this population (Kordsachia et al., 2017). As the direction of this relationship remains unclear, longitudinal studies may offer some insights into the interplay between emotion processing deficits and autobiographical memory dysfunction in the earliest stages of HD. Determining whether the valence and emotional re-experiencing of autobiographical memories are further altered in HD remains to be investigated and we suggest that studies incorporating phenomenological assessments will prove particularly informative in this regard (Irish, Lawlor, O'Mara, & Coen, 2011; Piolino et al., 2003). Moreover, it will be important to determine how the subjective experience of recollection is altered in HD and how this, in turn, impinges upon the individual's sense of self, given the close relationship between autobiographical memory retrieval and sense of continuity across subjective time (e.g., Prebble et al., 2013).

Interestingly, we did not find any significant epoch effects in relation to autobiographical memory performance in this study, resulting in a flat gradient across time periods in both HD and control participants. This finding is consistent with research in remote memory in HD, which has reported comparable profiles of both remote and recent memories for public events and famous faces (Albert et al., 1981; Beatty et al., 1988). Notably, however, previous studies of autobiographical memory using the AI in ageing and clinical populations have reported recency effects, whereby recently experienced events are recalled in significantly greater contextual detail relative to their remote counterparts (e.g., Esopenko & Levine, 2017; Levine et al., 2002). We tentatively suggest that our modification to the 'middle adulthood' period to accommodate for varying age groups in our sample may have influenced the profile of results, however, we note that similar findings to the current study have been documented in other dementia populations (e.g., Irish et al., 2011).

In terms of candidate mechanisms driving autobiographical memory disruption in HD, our correlational analyses did not reveal significant associations between the retrieval of internal details on the AI and neuropsychological indices of episodic memory, executive function, and phonemic fluency within the HD group. This finding is consistent with recent work that suggests that autobiographical memory performance is independent from laboratory tests of cognition (Esopenko & Levine, 2017). Moreover, our findings suggest that autobiographical memory deficits in HD cannot be explained solely by strategic retrieval or executive deficits. Replicating these findings with a more extensive battery of neuropsychological (and executive tests) will be important to further understand the specific cognitive mechanisms unpinning autobiographical memory disruption in HD.

From a clinical perspective, we did not observe significant differences in autobiographical memory function between people in the late premanifest or early manifest stages of HD, with both groups displaying marked autobiographical retrieval deficits relative to controls. This finding adds to a growing body of evidence for cognitive impairments in HD that occur prior to clinical diagnosis (Montoya et al., 2006; Robinson & Swanson, 1990; Solomon et al., 2007; Stout et al., 2011). Despite the lack of differentiation between late premanifest and manifest HD groups in terms of autobiographical memory performance, we did find an association between impaired retrieval of internal details (when probed) and more severe motor symptoms of HD. Together, this suggests the presence of autobiographical memory dysfunction in HD before motor symptoms reach the clinical threshold for diagnosis, with progressive degradation appearing as HD advances in disease severity. From a neuroanatomical perspective, we propose that autobiographical memory deficits likely reflect early atrophy in striatal regions and disruption of fronto-striatal circuitry (Vonsattel et al., 2011). This interpretation is consistent with recent findings from Esopenko and Levine (2017) who reported associations between decreased recall of internal details on the AI and

reductions in bilateral middle frontal white matter regions. Given the well-established role of the MTL in supporting contextually rich ABM retrieval (Moscovitch et al., 2016), it is further possible that hippocampal dysfunction, observed in the early stages of HD (Douaud et al., 2006; Rosas et al., 2003; van den Bogaard et al., 2011), contributes to the profiles of impairment observed here. Future studies incorporating structural neuroimaging metrics will be crucial to determine the neuroanatomical substrates of autobiographical memory disruption in HD as well as furthering our understanding of the role of subcortical regions in modulating memory performance in general.

This study is the first to uncover marked deficits in the ability to retrieve personally-defining memories from the recent and remote past in HD. How such deficits impinge upon the individual's sense of self and identity remains unclear and will be an important question to address in future studies (Prebble et al., 2013). Given that autobiographical memories serve important social functions through shared reminiscing and bonding on past experiences (Alea & Bluck, 2003; Kumfor et al., 2016), we propose that future studies exploring the link between autobiographical memory disruption and interpersonal function in HD will be crucial. Finally, given the well-established links between remembering the past and the capacity to envisage the future (Schacter, Gaesser, & Addis, 2013), it will be essential to understand how prospection and future-oriented thinking is potentially altered in HD, as has recently been demonstrated in other neurodegenerative disorders (Irish & Piolino, 2016). As the first study of autobiographical memory function in HD, our findings extend our understanding of the cognitive phenotype of HD.

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Supplementary Material

De-identified autobiographical interview excerpt from premanifest HD participant from childhood epoch (years 0-11) free recall.

time-internal other event-external
When I was 8, maybe 7 years old… I remember we'd just moved house. I grew up in
semantic semantic
(name of country). We lived in (name of country) for four years. We'd stayed at my
semantic event-internal
uncle's place up in (name of town) for the first few months. We went to the local
thought-internal perceptual-internal
show. I remember thinking I wanted to go on this ride. I can picture the kids sitting on
event-internal
the motorbike. I was the only one that managed to completely crash. I burnt my leg
event-internal
on the exhaust pipe.

Supplementary Table 1.

Mean internal detail (standard deviation) subcategories recalled by HD and control groups for free and probed recall conditions on the Autobiographical Interview.

Condition	Detail subcategory	HD	Control
Free Recall	Event	4.85 (2.53)	11.76 (4.64)
	Spatiotemporal	1.40 (.85)	2.76 (1.11)
	Perceptual	.62 (.94)	2.29 (1.63)
	Emotion	.67 (.98)	2.03 (1.59)
Probed Recall	Event	6.65 (2.81)	12.65 (4.31)
	Spatiotemporal	7.45 (1.44)	9.85 (1.83)
	Perceptual	3.68 (1.99)	6.99 (3.71)
	Emotion	2.84 (1.46)	4.99 (1.98)

HD = Huntington's disease.

Supplementary Table 2.

Mean external detail (standard deviation) subcategories recalled by HD and control groups for free and probed recall conditions on the Autobiographical Interview.

Condition	Detail subcategory	HD	Control
Free Recall	Semantic	3.67 (2.55)	2.74 (2.06)
	Repetition	.59 (.58)	.28 (.18)
	Other	1.39 (1.05)	1.05 (.97)
	External Event	.92 (1.52)	1.63 (3.23)
Probed Recall	Semantic	5.44 (3.40)	3.32 (2.24)
	Repetition	2.12 (1.62)	1.05 (.63)
	Other	3.18 (1.85)	1.63 (1.44)
	External Event	1.23 (1.66)	1.67 (3.27)

HD = Huntington's disease.

CHAPTER 4: MANUSCRIPT TWO – STRIATAL AND HIPPOCAMPAL CORRELATES OF AUTOBIOGRAPHICAL MEMORY IN HUNTINGTON'S DISEASE

4.1 Explanatory Notes for Manuscript Two

Whereas Manuscript One identified reductions in episodic autobiographical memory abilities in both late premanifest HD and early HD, Manuscript Two sought to identify the neural correlates underpinning autobiographical impairments. In order words, this manuscript aimed to address 'how' autobiographical memory impairments occur in HD, by examining select neural correlates.

We analysed the contribution of the striatum and hippocampus to autobiographical memory in this chapter. The hippocampus was chosen due to its well established role in a core network of structures involved in autobiographical retrieval, facilitating memory construction and elaboration (McCormick et al., 2013; Svoboda et al., 2006). We chose to also investigate striatal volume due to: i) early and pronounced atrophy that is seen in this region in premanifest HD making this a variable of interest within our participant sample, ii) evidence that has linked striatal volume to non-autobiographical anterograde memory disruption in HD (Solomon et al., 2007), and iii) recent evidence suggesting an important role for the anterior basal ganglia (i.e. striatum) in autobiographical memory performance (Esopenko & Levine, 2017) and iv) emerging research indicating that the striatum and hippocampus work in co-operation to facilitate episodic memory (Sadeh et al., 2011).

We addressed this theory driven approach of examining the striatum and hippocampus by incorporating manual tracing techniques. Although we acknowledge that autobiographical memory is supported by a much broader network of structures beyond just the striatum and hippocampus, we prioritised these structures of interest due to the supporting theory beforementioned, while working within the time limit constraints inherent to this thesis, with the over-arching aim of better understanding the role of striatal regions in supporting autobiographical memory.

This manuscript is under review in *Cortex*.

Striatal and Hippocampal Correlates of Autobiographical Memory Retrieval in Huntington's Disease

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Abstract

The capacity to retrieve personally experienced events across the lifespan, via autobiographical memory, has recently been shown to be disrupted in Huntington's disease (HD), a neurodegenerative disorder characterised by early, severe striatal degeneration, with associated cortical pathology gradually developing across the course of the disease. Autobiographical memory relies critically on the hippocampus and neocortical regions, whereas the importance of subcortical structures, such as the striatum, remains unclear. The aim of the current study was to determine the neural substrates of autobiographical memory deficits in HD by examining the relationship between volumes of striatal and hippocampal brain regions and autobiographical memory performance in HD. Thirty participants genetically confirmed to have the HD gene expansion (13 early diagnosed, 17 premanifest gene-carriers) and 24 controls completed the Autobiographical Interview (AI) as an index of contextually rich autobiographical memory across the lifespan. Regional brain volumes of the striatum and hippocampus were derived from manual tracing of magnetic resonance images (MRI). HD groups showed impaired autobiographical retrieval across all time periods relative to controls. As expected, we observed atrophy in the caudate and putamen of HD participants. While caudate atrophy was related to impaired free recall of total internal (episodic) details, smaller striatal structures (both caudate and putamen) and the hippocampi were related to impaired probed recall. These findings support a growing body of evidence suggesting a striatal contribution to autobiographical memory retrieval. Clinically, our findings suggest that autobiographical dysfunction may be an overlooked feature of patient populations with subcortical atrophy.

Keywords: subcortical, episodic memory, dementia, MRI volumetry.

Autobiographical memory impairments are a pervasive feature of many neurodegenerative disorders including Alzheimer's disease (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012; Irish et al., 2011), frontotemporal dementia (Irish et al., 2014; Piolino et al., 2003), motor neuron disease (Hsieh et al., 2016), and posterior cortical atrophy (Ahmed et al., 2018). Recently, our group reported significant autobiographical memory dysfunction in both the late premanifest and early manifest stages of Huntington's disease (HD) (Carmichael, Irish, Glikmann-Johnston, Singh, & Stout, 2019). HD is a rare autosomal dominant disorder that causes progressive cognitive, motor, and psychiatric disturbances, along with brain atrophy that disproportionately affects the caudate nuclei and putamen in the brain's striatum (Walker, 2007).

Autobiographical memory refers to the retrieval of personally-relevant experiences within a specific time and place, comprising sensory-perceptual details as well as self-referential and general semantic knowledge, which includes personal facts from across the lifespan. Both episodic retrieval of experiences, and semantic self-knowledge are important to a person's sense of self across time (Prebble, Addis, & Tippett, 2013; Strikwerda-Brown, Grilli, Andrews-Hanna, & Irish, 2019). Autobiographical memory deficits in neurodegenerative disorders and healthy ageing are typically ascribed to degeneration within a core brain memory network encompassing medial temporal (including the hippocampus), posterior parietal, and prefrontal regions (Cabeza & St Jacques, 2007; Svoboda, McKinnon, & Levine, 2006). The involvement of subcortical regions in autobiographical memory, including the striatum and middle frontal white matter tracts, by contrast, remains less well understood. An emerging line of research on traumatic brain injury, however, suggests an important striatal contribution (Esopenko & Levine, 2017). These findings are relevant in the current context as early and severe striatal degeneration is a hallmark of HD (Vonsattel,

Keller, & Ramirez, 2011). No study to date, to our knowledge, has directly examined the relationship between striatal atrophy and autobiographical memory in HD.

In people with the HD CAG expansion, neuropathological changes begin in the striatum during the premanifest period, prior to when HD is clinically diagnosed. By neurological convention, diagnosis only occurs once unequivocal motor signs have been detected by a clinician (Walker, 2007). Because the HD CAG expansion can be identified at any time in life, people with the HD genotype can be systematically studied prior to emergence of the phenotype, creating a picture of the continuum from neurological health to impairment, across clinical and neuroimaging assessments. Evidence shows that in addition to HD's manifestation in the striatum, early neurodegeneration occurs in other brain regions important for autobiographical memory, including the thalamus, hippocampus, and amygdala (Ahveninen, Stout, Georgiou-Karistianis, Lorenzetti, & Glikmann-Johnston, 2018; Georgiou-Karistianis, Scahill, Tabrizi, Squitieri, & Aylward, 2013; Rosas et al., 2003). The magnitude of structural changes in these non-striatal regions is lower, however, than the striatal atrophy observed in HD (Glikmann-Johnston, Fink, Deng, Torrest, & Stout, 2019; Vonsattel et al., 2011).

Until recently, the status of autobiographical memory in HD was unknown (Carmichael et al., 2019), and the neural substrates of these impairments have not yet been determined. Neuroimaging studies of episodic memory for word-list and story learning in HD have revealed associations between impaired ability to learn and retrieve new information and striatal degeneration (Campodonico et al., 1998; Harrington et al., 2014; Solomon et al., 2007; Starkstein et al., 1992). The association between impaired episodic memory on word-list learning tasks and the striatum has been linked to the role of fronto-striatal circuitry in the executive aspects of successful memory retrieval (Solomon et al., 2007). By this view, striatal atrophy in HD would likely disrupt executive aspects of autobiographical retrieval,

particularly with freely recalling personal memories, which require executive cognition for memory search and strategic retrieval functions (Tremont, Halpert, Javorsky, & Stern, 2000). The role of the hippocampus is well-established in both the construction and elaboration of episodic autobiographical information (McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2013). Recent evidence, however, suggests that the striatum contributes to the formation of episodic memories in co-operation with the hippocampus, with greater striatal activity during episodic encoding of items that are remembered compared to items that are forgotten (Sadeh, Shohamy, Levy, Reggev, & Maril, 2011). It has thus been proposed that the striatum may mediate prefrontal involvement in episodic memory operations (Sadeh et al., 2011). By this view, degeneration in striatal regions, as seen in HD, may disrupt the ability to encode and retrieve autobiographical information.

Given our recent findings of pervasive autobiographical memory impairments in late premanifest and early HD (Carmichael et al., 2019), the aim of the current study was to examine the association between striatal atrophy and autobiographical memory performance on the Autobiographical Interview (AI; Levine et.al, 2002) in HD. As the hippocampus is strongly implicated in autobiographical memory retrieval, and given evidence of hippocampal dysfunction with disease progression in HD (Vonsattel et al., 2011), we further explored the relative contribution of the hippocampus in autobiographical memory performance in HD.

Materials and Methods

Participants

We tested 30 HD participants, including 13 with early manifest HD, 17 who were premanifest HD gene expansion carriers, and contrasted their performance with 24 healthy controls. All HD participants were genetically confirmed to carry the HD CAG expansion. Healthy control participants were required to have no known family history of HD *or* be

confirmed gene-negative. Exclusion criteria for all participants included diagnosis of a severe psychiatric condition, history of drug or alcohol abuse, and limited English proficiency (because of language demands of the autobiographical memory task).

All HD participants had a Total Functioning Capacity ≥ 7 suggesting minimal to moderate clinical impairments (Huntington Study Group, 1996). Premanifest HD participants were estimated to be within 16 years to clinical diagnosis based on the Langbehn et al. (2004) formula (21.54 + Exp (9.556 – 0.1460 x CAG) - age), with an average of 6.88 years to predicted diagnosis. The severity of HD symptoms in manifest and premanifest HD participants was assessed using the Unified Huntington's Disease Rating Scale (UHDRS: Huntington Study Group, 1996). As anticipated, compared to premanifest HD, manifest HD participants had more severe motor signs and a lower score on the functional capacity assessment. The combined HD group (n = 30) did not differ from the control group in terms of age, but when we stratified the sample into premanifest and manifest subgroups, the manifest group was on average older than the premanifest HD group (p = .004). Otherwise, the groups did not differ in terms of sex, education, and premorbid intelligence estimates (Table 1).

We recruited participants through the Statewide Progressive Neurological Disease Service at Calvary Health Care Bethlehem Hospital and from our internal research volunteer database held at Monash University (Clayton, Australia). We obtained ethics approval from the Monash University Human Research Ethics Committee and Calvary Health Care Bethlehem Research Ethics Committee. Participants provided written informed consent before participating in the study, and we offered reimbursement to cover travel cost and time.

Table 1.

Means ± Standard Deviations (Range) for select demographic and clinical information for HD (manifest and premanifest) and control participants.

	Manifest HD (n = 13)	Premanifest HD (n = 17)	Control (n = 30)	*p*-Value	Group Differences
Sex (F:M)	4:9	10:7	12:12	-	-
Age	54.62 ± 7.91 (43-66)	46.53 ± 7.41 (36-56)	50.13 ± 7.55 (39-65)	.02	Manifest HD > Premanifest HD
Education	14.65 ± 2.70 (9-18)	14.88 ± 3.57 (10-22)	16.52 ± 3.72 (8-23)	.19	-
Estimated FSIQ	107.9 ± 9.68 (95-123)	108.64 ± 7.51 (97-126)	110.14 ± 9.78 (91-127)	.75	-
CESD-R	8.46 ± 9.49 (0-29)	5.65 ± 7.76 (0-30)	8.29 ± 9.33 (0-37)	.59	-
DBS	347.69 ± 61.10 (228-485)	291.26 ± 67.57 (186-420)	-	.025	Manifest HD > Premanifest HD
UHDRS TMS	19.18 ± 9.54 (9-40)	1.06 ± 2.14 (0-7)	-	<.001	Manifest HD > Premanifest HD
UHDRS TFC	10.23 ± 2.20 (7-13)	12.76 ± .56 (11-13)	-	<.001	Premanifest HD > Manifest HD
RAVLT Delay	7.23 ± 2.80 (3-12)	9.18 ± 3.05 (2-15)	12.17 ± 2.12 (8-15)	<.001	Control > Premanifest HD > Manifest HD
RAVLT Recognition	12.69 ± 2.36 (8-15)	13.88 ± 1.62 (9-15)	14.63 ± .71 (12-15)	.003	Control > Manifest HD
SDMT	36.15 ± 10.24 (18-51)	51.47 ± 12.63 (34-78)	59.42 ± 8.64 (39-72)	<.001	Control > Premanifest HD > Manifest HD
Verbal Fluency	41.77 ± 15.78 (17-63)	43.71 ± 13.61 (24-70)	50.58 ± 9.95 (37-77)	.90	-

Abbreviations: HD = Huntington's disease; FSIQ = full scale intelligence quotient; CESD-R = Center for Epidemiologic Studies Depression Scale-Revised; DBS = Disease Burden Score; UHDRS = Unified Huntington's Disease Rating Scale; TMS = Total Motor Score; TFC = Total Functioning Capacity; RAVLT = Rey Auditory Verbal Learning Test; SDMT = Symbol Digit Modalities Test. *P*-Value based on univariate analysis of variance except for DBS, UHDRS TMS and UHDRS TFC which are based on independent samples t-tests. Group differences based on significant (p <.05) Bonferroni post-hoc tests.

Behavioural Measures

Autobiographical interview. We administered the Autobiographical Interview (AI; Levine et al., 2002) following standard procedures, as detailed in Carmichael et al. (2019). Briefly, participants were asked to recall spatiotemporally specific personal events from five life epochs: early childhood (0-11), teenage years (11-17), early adulthood (18-30), middle adulthood (31-55), and the past 12-months. As previously reported in Carmichael et al. (2019), due to the age range of our participants (31-66), the 'middle adulthood' epoch of our study, which is typically considered to be between the ages 31-55 was modified for participants under 55 years of age, whereby they were asked to retrieve an event that occurred

after the age of 31, but *not within* the last 12-months to minimise overlap with the most recent period.

We assessed autobiographical memory for free recall (extemporaneous), and using general probing (clarification of instructions), and specific probing (structured interview to elicit maximum contextual details). Consistent with the standard protocol (e.g., Levine et al., 2002), we combined the free recall and general probe conditions, hereafter referred to as 'free recall'. Free recall, general probed, and probed recall conditions were combined to create the 'probed recall' composite score.

Briefly, transcribed protocols were segmented into information details, and were classified as *internal* or *external. Internal* details were defined as episodic in nature (specific to a time and place), pertaining to the main event described, and were assigned to one of four categories: event details, spatiotemporal details (time and place details combined), perceptual details, and emotion/thought details. *External* details reflected details not directly related to the main event. In this study, we focus on *internal* details as an index of episodic retrieval from autobiographical memory.

Cognitive and clinical characterisation. We administered a battery of neuropsychological tests to measure premorbid IQ (National Adult Reading Test 2nd Edition; NART-2: Nelson & Willison, 1991), and as a reference to overall cognitive functioning. Specifically, we assessed verbal memory using the Rey Auditory Verbal Learning Test (RAVLT: Schmidt, 1996), which is a 15-item word-list learning task followed by a 30-minute delayed free recall and recognition test. To assess visual attention and processing speed, we used the Symbol Digit Modalities Test (SDMT; Smith, 1982). Verbal fluency was assessed using letter fluency from the Controlled Oral Word Association Task, which required people to generate as many words as possible beginning with a particular letter of the alphabet within one minute. In addition to neuropsychological testing, participants rated

their depression symptoms on the Centre for Epidemiological Studies Depression Scale Revised (CESD-R; Eaton, Smith, Ybarra & Muntaner, 2004), which we considered to be a key covariate due to the established link between depression and autobiographical memory deficits (Williams et al., 2007), and depression and HD (Paulsen, Ready, Hamilton, Mega, & Cummings, 2001).

Imaging

Image acquisition and pre-processing. High resolution MRI data were acquired using a Siemens 3 Tesla (3T) MRI with 32-channel head coil at Monash Biomedical Imaging (Clayton, Australia). Acquisition parameters for the T1-weighted images consisted of 192 slices, voxel size 1 mm x 1mm x 1mm, 9° flip angle. Using SPM12 (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011), T1-weighted images were bias corrected, linearly registered with 6 degrees of freedom to the MNI 1mm nonlinear template, and resliced. Images were de-identified prior to volumetric analysis to minimise any bias.

Volumetric analysis. The caudate, putamen and hippocampus were manually delineated using ITK-SNAP, which enabled simultaneous display of coronal, sagittal, and axial images (Yushkevich et al., 2006). Manual segmentation of left and right caudate and putamen was performed in the axial plane using a validated protocol previously described in detail (Looi et al., 2008; Looi et al., 2009), and with reference to a standard atlas (Duvernoy, 2012). The left and right hippocampi were traced in the coronal plane using a well-validated protocol (Watson et al., 1992). The total volumes for each brain structure (left and right separately) were calculated by summing the number of voxels across all slices traced.

We were blinded to group membership during the manual tracing. To establish inter-rater relatability, seven randomly selected images were independently traced by a second rater. Striatal structures (caudate, putamen) were traced by AMC and reliability tracing was completed by YG-J. Intra-class correlation coefficient (ICC) values were .97 for left caudate,

.99 for left putamen, .98 for right caudate, and .99 for right putamen. The hippocampi were traced by YG-J and ECM, and ICCs were .98 for left hippocampus and .98 for right hippocampus.

Statistical Analyses

Data were analysed using IBM-SPSS Version 25. To investigate group differences in structural volume, we ran a 3 (group: manifest HD, premanifest HD, controls) x 3 (structure: caudate, putamen, hippocampus) x 2 (hemisphere: left, right) ANCOVA controlling for total intracranial volume (ICV), followed by Sidak post-hoc tests. Next, to determine differences in autobiographical recall, we conducted a 3 (group: manifest HD, premanifest HD, controls) x 5 (epoch: early childhood, teenage years, early adulthood, middle adulthood, and the last 12-months) repeated measures ANOVA for free and probed recall separately, followed by Sidak post-hoc tests. Effect sizes are reported, where appropriate, using eta-squared. To determine the relationship between brain volumes and internal autobiographical details we ran a series of partial correlations controlling for ICV. Finally, we conducted exploratory partial Pearson correlations between subcategories of internal details (event, spatiotemporal, perceptual, emotion/thought) and structure volumes controlling for ICV, setting a conservative significance threshold of $p = .01$.

Results

Our primary aim was to investigate the relationship between brain volumes (specifically the striatum and the hippocampus) and autobiographical memory performance in HD. In this section, we first report the volumes of brain structures (i.e., caudate, putamen, hippocampus) across each group to examine consistency with previously literature. Second, we report key outcomes from the AI as a background to our primary analyses. Third, we report analyses for our key aim, which was examining the relationship between autobiographical memory performance and volumes of the caudate, putamen and

hippocampus. We used a combined group of premanifest and manifest HD participants (n=30) because these groups did not differ in their performance on key autobiographical variables (consistent with findings from Carmichael et al., 2019 using a subset of the current data), and because of the relatively small sample sizes. Further, as we did not find differences in the number of internal details recalled across epochs in our HD group, we averaged the internal details together to form free and probed recall composites (see also Esopenko & Levine, 2017). Finally, we report results from exploratory analyses of the subcategories of episodic (internal) autobiographical details from the AI.

Comparison of Brain Volumes Between Groups

As expected, our analysis yielded a significant group x structure interaction, $F(4,100) = 27.18$, $p < .001$, $\eta p^2 = .52$, with manifest and premanifest HD groups displaying smaller caudate and putamen volumes compared to the control group (all *p*s <.003). The degree of striatal atrophy in HD was graded, with manifest HD displaying smaller caudate and putamen volumes compared to the premanifest HD group (all *ps* < .003). Hippocampal volumes did not differ significantly between groups ($p = .17$). We did not observe a main effect of hemisphere (right, left), nor any group x hemisphere, or group x hemisphere x structure interactions (all *p*s > .34). Due to finding no main effects or interactions involving hemisphere, we summed each left and right structure for subsequent analyses. See Table 2 for descriptive data on MRI volumes.

Within the combined HD sample (n = 30), both caudate and putamen atrophy were associated with greater disease burden (caudate: $r = -.44$, $p = .023$; putamen: $r = -.71$, $p < .001$) and more severe motor signs (caudate: $r = -.67$, $p < .001$; putamen: $r = -.65$, $p < .001$). Hippocampal volume was not significantly associated with disease severity measures.

Table 2.

Means ± Standard Deviations (range) of caudate, putamen, and hippocampal volumes (mm^3) in manifest HD, premanifest HD, and control groups.

		Manifest HD (n = 13)	Premanifest HD (n = 17)	Controls (n = 24)	p-Value	Significant group differences
Hippocampus	L	2678.08 ± 377.52 (1965-3209)	2948.06 ± 359.85 (2262-3752)	2752.21 ± 349.31 (2232-3551)	.12	-
	R	2928.15 ± 451.21 (2372-3633)	3140.18 ± 421.34 (2443-3827)	2963.29 ± 311.88 (2393-3758)	.31	-
	Total	5606.23 ± 798.70 (4455-6727)	6088.23 ± 760.72 (4708-7579)	5715.50 ± 624.11 (4662-7262)	.17	-
Caudate	L	2646.85 ± 668.47 (1902-4070)	3600.24 ± 654.24 (2219-4917)	4167.54 ± 536.61 (2951-5006)	<.001	Control > Premanifest HD > Manifest HD
	R	2881.08 ± 685.72 (2139-4098)	3768.88 ± 732.13 (2287-5460)	4353.67 ± 550.29 (2987-5368)	<.001	Control > Premanifest HD > Manifest HD
	Total	5527.92 ± 1341.56 (4041-8168)	7369.12 ± 1380.77 (4506-10377)	8521.21 ± 1054.93 (5938-10118)	<.001	Control > Premanifest HD > Manifest HD
Putamen	L	2283.69 ± 636.20 (1390-3464)	3039.00 ± 519.17 (2287-3849)	3891.63 ± 604.42 (2695-5056)	<.001	Control > Premanifest HD > Manifest HD
	R	2380.85 ± 602.03 (1616-3345)	3027.35 ± 600.23 (2006-4055)	3876.46 ± 494.23 (3027-4720)	<.001	Control > Premanifest HD > Manifest HD
	Total	4664.54 ± 1230.38 (3050-6809)	6066.35 ± 1102.74 (4309-7904)	7768.08 ± 1063.34 (6076-9629)	<.001	Control > Premanifest HD > Manifest HD

Abbreviations: HD = Huntington's disease. *P*-Value based on univariate analysis of covariance (controlling for ICV) for hippocampus, putamen and caudate comparisons. Group differences based on Sidak post-hoc tests.

Autobiographical Memory Performance

Free recall. Consistent with previous findings (Carmichael et al. 2019), a repeated measures ANOVA revealed a main effect of group, $F(2,51) = 24.96$, $p < .001$, $\eta p^2 = .49$, with both manifest and premanifest HD groups recalling fewer internal (episodic) autobiographical details compared to controls (*p*s <.001). HD groups did not differ from one another ($p = .77$). We did not find an epoch x group interaction, $F(8,204) = .39$, $p = .93$, or a main effect of epoch ($p = .07$). A similar pattern of results was obtained when we controlled for age in the analyses. See Figure 1.

Probed recall. A main effect of group was again detected, $F(2,51) = 19.97$, $p < .001$, $\eta p^2 = .44$, with both HD groups retrieving fewer internal details compared to controls (*p*s <.001). As before, the manifest HD and premanifest HD groups did not differ significantly

from one another (p = .40). We did not detect a main effect of epoch, $F(4,204) = 1.15$, p = .33, or an epoch x group interaction $F(8,204) = .49$, p = .86. See Figure 1.

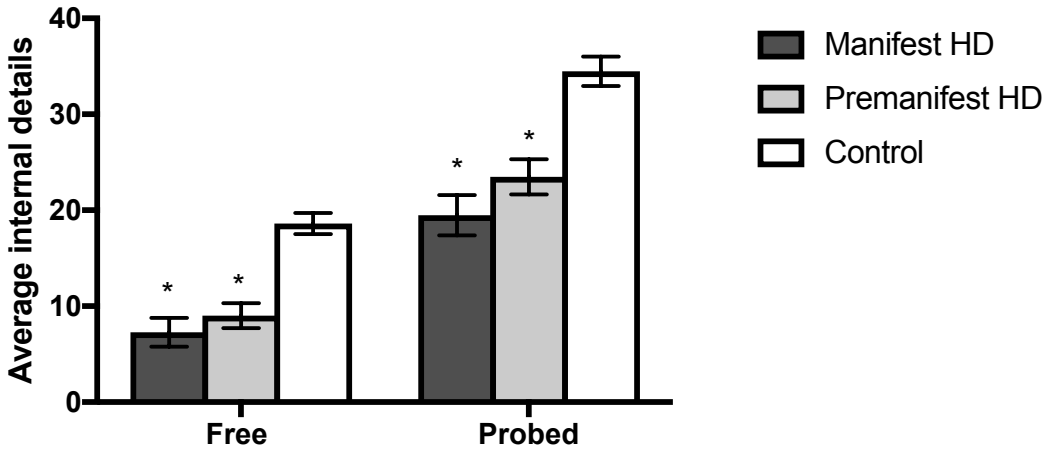

Figure 1. Mean internal (episodic) details retrieved on the Autobiographical Interview (AI) summed across epochs for free recall (left) and probed recall (right) conditions. Error bars represent standard error of the mean. * $p < .001$, representing differences between HD groups and control group.

Relationship Between Internal Autobiographical Details and Brain Volumes

Combined HD group (n = 30). Poorer *free* recall of internal details was found to relate to smaller caudate volumes (r = .43, p = .010), and trended towards significance with putamen (r = .38, p = .022) and hippocampal (r = .35, p = .033) volumes. See Figure 2. For *probed* recall, smaller volumes of all brain structures related to poorer retrieval of internal details (caudate: r = .53, p = .001; putamen: r = .45, p = .007; hippocampus: r = .45, p = .007). See Figure 3.

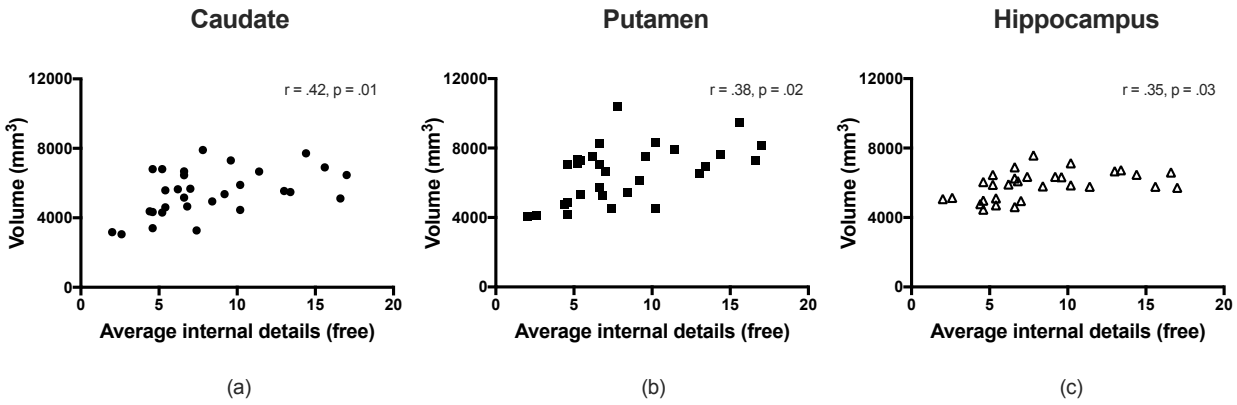

Figure 2. Relationship between average free internal details and summed left and right volumes of the: (a) caudate, (b) putamen, and (c) hippocampus in HD participants (n = 30).

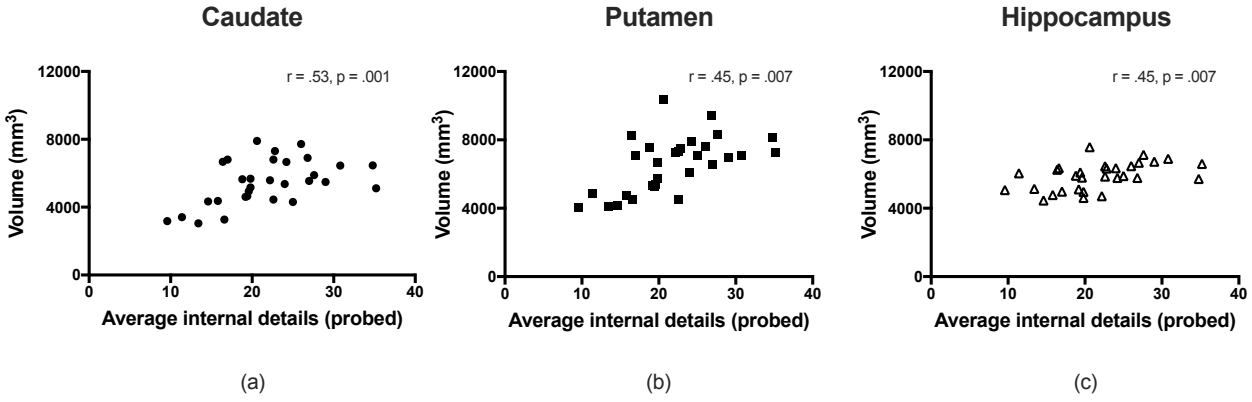

Figure 3. Relationship between average probed internal details and summed left and right volumes of the: (a) caudate, (b) putamen, and (c) hippocampus in HD participants (n = 30).

Control participants. Trend associations emerged between both free and probed internal details and putamen (free: $r = .43$, $p = .021$; probed: $r = .44$, $p = .017$) and hippocampal (free: $r = .46$, $p = .013$; probed: $r = .46$, $p = .014$) volumes. No associations were found between the caudate and internal details in controls ($ps > .24$).

Relationship Between Internal Detail Subcategories and Brain Volumes in HD

Focusing only on the correlations that survived the conservative significance threshold, for *both free and probed* total recall in HD, we next explored associations between the internal detail subcategories on the AI and brain volumes.

Event details were found to correlate with volume of the caudate (free: $r = .45$, $p = .007$; probed: $r = .49$, $p = .003$) and putamen (free: $r = .43$, $p = .009$; probed: $r = .45$, $p = .007$). *Perceptual details* were associated with hippocampal volumes across free ($r = .44$, $p = .009$) and probed ($r = .47$, $p = .005$) conditions. No other significant associations were detected between brain volumes and retrieval of spatiotemporal or emotion/thought details.

Discussion

The retrieval of contextually rich autobiographical memories involves a number of cognitive processes supported by a distributed neural network. Although the hippocampus is a well-established component of the core autobiographical network, crucial for facilitating memory construction and elaboration (McCormick et al., 2013), more recent work suggests that striatal regions may play a role in autobiographical retrieval (Esopenko & Levine, 2017). In the current study, we investigated the association between striatal and hippocampal brain volumes and autobiographical retrieval in HD, which is characterised by early and pronounced striatal atrophy. Overall, we found that caudate atrophy was associated with poorer autobiographical memory across both *free* and *probed* conditions, whereas the putamen and hippocampus emerged as correlates of *probed* recall only. We discuss these findings in relation to a growing body of research that emphasises the cooperation between the striatum and hippocampus during episodic memory (e.g., Ben-Yakov & Dudai, 2011).

Mounting evidence indicates an important role for the striatum in modulating episodic memory performance (Murty, DuBrow, & Davachi, 2015; Sadeh et al., 2011), however

formal investigation of the effects of striatal damage on autobiographical memory retrieval has been scarce. In this study, we demonstrated that in HD, degeneration of striatal regions, particularly the caudate, is associated with compromised recollection of personally salient memories. Moreover, this effect was observed across both free and probed retrieval conditions. Our findings using a validated autobiographical memory interview are consistent with previous studies in HD which have used classic word-list learning tasks, replicating the associations between striatal atrophy and impaired episodic retrieval (e.g., Solomon et al., 2007). Degeneration of the caudate would be expected to weaken the integrity and impair function of the fronto-striatal brain circuits, which are implicated in free recall autobiographical memory retrieval (Buckner, 2003; Fletcher & Henson, 2001). Future studies will be needed to define the strategic retrieval, verification and monitoring of information during autobiographical retrieval in HD, and how these functions are affected in relation to diminished striatal-prefrontal connectivity.

Whereas impairments in free recall of information are closely linked to frontal regions of the brain (as well as fronto-striatal circuitry), probed recall is proposed to reduce demands on frontal brain regions by circumventing the need to rely on extensive strategic search processes (Irish et al., 2014; Moscovitch, Cabeza, Winocur, & Nadel, 2016). In the current study, we found that the provision of structured probing was not sufficient to ameliorate autobiographical memory dysfunction in HD (see also Carmichael et al., 2019), consistent with findings in other neurodegenerative populations with autobiographical memory impairments (Irish et al., 2011). Interestingly, probed retrieval in the HD group was found to correlate with both striatal and hippocampal integrity, reinforcing current accounts which propose that episodic memory is supported by striatal-hippocampal interactions (Ben-Yakov & Dudai, 2011; Sadeh et al., 2011).

Our finding of a significant association between hippocampal volumes and probed, but not free, recall in HD fits well with the contention that the hippocampus is important for the elaboration of autobiographical memories in rich contextual detail (McCormick et al., 2013). Despite the purported role of the hippocampus in facilitating elaboration of autobiographical narratives, we did *not* detect a significant difference in hippocampal volumes in either the premanifest or manifest HD groups compared to controls. Some studies of early manifest HD *have* detected total hippocampal volume reductions using automated volumetry (Vonsattel et al., 2011) and methodological differences in tracing techniques may account for some of these discrepancies. Thus, although we did not find differences in hippocampal volumes between the groups, it remains likely that the hippocampi are affected in HD, given recent work highlighting shape differences in the hippocampi in early stages of HD compared to controls (van den Bogaard et al., 2011). Importantly, volumetric analyses have limited capability to highlight differences that are better examined by functional neuroimaging techniques, which can, for example reveal reduced connectivity with other key nodes of the core autobiographical network. We suggest that the use of multimodal neuroimaging techniques to capture alterations in shape, structural and functional connectivity of the hippocampus will be an important future direction for this line of work.

Finally, we found preliminary evidence for associations between specific subcategories of internal details and the striatum in both free and probed retrieval conditions. Notably, striatal atrophy was associated with recalling fewer *event* details, which are those details pertaining to the main episode being described. We tentatively suggest that striatal atrophy, and in turn diminished efficiency of the fronto-striatal circuits, may compromise strategic search and verification processes, which could result in gist-based retrieval, a possibility that will need to be tested in future studies. In contrast to the striatal association with event details, the hippocampus volume was associated with perceptual details in both the

free and probed conditions in the HD group. This finding associating hippocampal volumes with the recall of rich sensory-perceptual detail resonates with prominent theoretical frameworks in which the hippocampus is posited to curate the retrieval of perceptual elements stored in posterior parietal regions into a spatially coherent framework (Ramanan et al., 2018; Rubin, 2006; Sheldon & Levine, 2016). To better understand the relationship between retrieving specific episodic details and neural pathology in HD, we further suggest that it will be important to explore how degeneration of other structures, including the amygdala, which is atrophied in both premanifest and manifest HD (Ahveninen et al., 2018), disrupts *emotional* aspects of autobiographical recollection in HD.

This study is the first, to our knowledge, to demonstrate an association between striatal degeneration and the ability to retrieve episodic autobiographical details under conditions of low and high retrieval support (free vs probed recall). Autobiographical memory is not routinely assessed in clinical settings. Our finding that autobiographical memory is affected early in HD, and associated with pathological volume loss in the caudate nucleus, may suggest that autobiographical memory impairments are an overlooked early cognitive sign in HD, overshadowed by the canonical motor, attentional, and executive difficulties. Given the relevance of autobiographical memory for sustaining social relationships (Bluck, Alea, Habermas, & Rubin, 2005), consideration of the clinical impact of our findings is warranted. Further, our findings shed new light on the possible neural substrates of autobiographical memory dysfunction in HD and corroborate a growing literature emphasising striatal-hippocampal interactions in the service of episodic recollection.

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CHAPTER 5: MANUSCRIPT THREE – DISCRETE CHANGES TO THE FREQUENCY AND FUNCTION OF AUTOBIOGRAPHICAL REMINSICENCE IN HUNTINGTON'S DISEASE

5.1 Explanatory Notes for Manuscript Three

While Manuscript One and Two focus on the objective understanding autobiographical memory from a cognitive and neural perspective, Manuscript Three examines the perceived functional utility of autobiographical memory in HD, that is, 'why' do people living with HD engage in autobiographical reminiscence. Autobiographical reminiscence has been proposed to serve important functions that shift dynamically across the lifespan dependant on varying life roles and changing circumstances. In this manuscript, we examined the frequency that people living with HD self-report thinking and talking about the past, and how often they perceived using autobiographical reminiscence for social bonding, self-continuity and for guiding and directing future behaviour.

HD participants completed a questionnaire to investigate the reasons they engage in autobiographical reminiscence. Beyond the objective data collected in Manuscript One and Two, Manuscript Three provides complimentary subjective data based on the perceived experience of people living with HD.

This chapter has been revised and resubmitted to *Memory* following minor changes.

Discrete Changes to the Function and Frequency of Autobiographical Reminiscence in Huntington's Disease

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Abstract

Autobiographical memory is widely posited to serve self, social and directive functions. Recent evidence suggests marked autobiographical memory impairments in Huntington's disease (HD), however, no study to date has determined how the perceived functions of autobiographical reminiscence may be altered in HD. The current study aimed to assess the self-reported frequency and function of autobiographical reminiscence in HD. We assessed autobiographical reminiscence in late premanifest (n=16) and early stage HD (n=14), relative to healthy controls (n=30). Participants completed the Thinking About Life Experiences Scale Revised (TALE-R), which measures three putative functions of autobiographical memory (self, social, directive) and a measure of self-rated depressive symptomology. People with manifest HD reported *talking* less frequently about the past compared to controls. In contrast, no group differences were found in terms of *thinking* about the past. Manifest HD participants further reported using their autobiographical memories for social functions less frequently compared to controls. No other differences were evident in terms of self or directive functions of autobiographical memory. These self-report findings complement recent reports of autobiographical memory disruption on performance-based tasks in HD. Future studies exploring how changes in autobiographical reminiscence impact a sense of self continuity in HD will be important in this regard.

Keywords: reminiscence, autobiographical memory, the self, social, communication

Huntington's disease (HD) involves neuropsychiatric and cognitive symptoms, which can emerge 10-15 years prior to the onset of clinically-significant motor symptoms (Stout et al., 2011). Episodic memory impairments are well-established in HD, encompassing both anterograde (El Haj, Caillaud, Verny, Fasotti, & Allain, 2016; Montoya et al., 2006; Solomon et al., 2007; Stout et al., 2011) and retrograde (Beatty, Salmon, Butters, Heindel, & Granholm, 1988) memory. Crucially, a recent study from our group reveals that these impairments extend to the retrieval of autobiographical memories (Carmichael, Irish, Glikmann-Johnston, Singh, & Stout, 2019). Autobiographical memory refers to the multifaceted capacity to recollect personally relevant events from the past in rich sensory-perceptual detail (Conway & Pleydell-Pearce, 2000). Autobiographical memories are often imbued with visual imagery and strong emotional connotations, giving rise to a sense of reliving the original event, via a self-knowing or *autonoetic* form of consciousness (Irish, Lawlor, O'Mara, & Coen, 2011; Wheeler, Stuss, & Tulving, 1997). Thinking and talking about autobiographical memories (i.e., reminiscing) can serve a number of core functions including: 1) maintenance of a coherent sense of self and identity over time (*self*-function); 2) facilitation of social-bonding and intimacy in relationships through shared experiences (*social*-function), and 3) guiding present and future thinking and behaviour (*directive*-function) (Bluck & Alea, 2011; Bluck, Alea, Habermas, & Rubin, 2005; Pillemer, 1992). For people with HD, the functions that autobiographical reminiscence serve in the context of declining autobiographical memory, remains unknown.

In general, the functions of autobiographical reminiscence shift dynamically over the lifespan, dependent on varying life roles and changing circumstances (Bluck & Alea, 2009). Consequently, studies show that the self-reported functions of autobiographical reminiscence are affected by factors including age (Alea, Bluck, & Ali, 2015; Bluck & Alea, 2009; Harris, Rasmussen, & Berntsen, 2014), life satisfaction (Cappeliez, O'Rourke, & Chaudhury, 2005),

and mood (del Palacio-Gonzalez, Watson, & Berntsen, 2018; Grace, Dewhurst, & Anderson, 2016). Studies in healthy ageing indicate that autobiographical reminiscence most frequently serves social functions (Bluck & Alea, 2009; Harris et al., 2014). These findings demonstrate the social utility of autobiographical memory in everyday life, in that it allows people to think and talk about memories to foster intimacy, closeness, and to maintain conversation (Alea & Bluck, 2003; Harris et al., 2014). In older adults, higher levels of life satisfaction have been associated with the social functions aspects of autobiographical reminiscence (Cappeliez et al., 2005), which suggests that this function of autobiographical reminiscence likely serves adaptive purposes as we age. Mood has been demonstrated to influence the 'self' function of autobiographical reminiscence, with findings suggesting that depressive symptomology in healthy samples is associated with increased reminiscence for self-focused reasons (Grace et al., 2016). Mood has been further associated with the frequency of autobiographical reminiscence, with increased depressive symptoms associated with a combination of higher levels of *thinking* about the past and lower levels of *talking* about the past (Grace et al., 2016).

Autobiographical memory dysfunction is a core feature of many neurodegenerative disorders (Irish, Hornberger, et al., 2011; Piolino et al., 2003), resulting in impoverished accounts of formerly evocative events (Irish, Lawlor, O'Mara, & Coen, 2010). Moreover, autobiographical memory dysfunction has been linked to changes in identity and sense of personhood in Alzheimer's disease (Addis & Tippett, 2004; Strikwerda-Brown, Grilli, Andrews-Hanna, & Irish). In HD, pervasive episodic autobiographical memory impairments have been detected both in the late premanifest and early manifest stages of HD, disrupting the retrieval of both remote and recent personal memories (Carmichael et al., 2019). Despite these findings, few studies have directly examined the self-reported functions of autobiographical memory in neurodegenerative populations. One study demonstrated

comparable self-reported use of autobiographical memories for *self* (identity) and *social* (conversation) functions in Alzheimer's disease and healthy controls (El Haj & Antoine, 2016). Interestingly, the Alzheimer's disease group reported using reminiscence as a means of death preparation (i.e., coming to terms with their own mortality) and boredom reduction (i.e., for something to do to pass the time) more often than controls. These findings are in keeping with recent studies of spontaneous cognition (e.g., mind wandering) suggesting that some aspects of internal mentation remain relatively preserved in Alzheimer's disease (O'Callaghan, Shine, Hodges, Andrews-Hanna, & Irish, 2019).

Understanding how and why people with HD engage in autobiographical reminiscence, in the context of disrupted autobiographical recollection, is central to enhancing our understanding of the internal thought processes and lived experience of people in different stages of the disease. Moreover, this line of enquiry may inform the use of targeted psychosocial interventions to improve interpersonal function in HD. As such, we aimed to determine the perceived frequency and function of autobiographical reminiscence in premanifest and manifest HD compared to control participants. We were interested in both the premanifest period of HD, when subtle cognitive and motor signs of disease are beginning to emerge but insufficient for clinical diagnosis, and in early manifest disease, when a diagnosis of HD, which is based on the unequivocal presence of HD motor signs, has already occurred.

Method

Participants

Thirty participants who were Huntington's disease gene-expansion carriers (CAG repeat length ≥ 39) were recruited for this study, including 14 with early stage HD (i.e., manifest HD) and 16 in the premanifest stage (i.e., premanifest HD), and we compared their performance to 30 healthy controls. Manifest HD participants had minimal to moderate

clinical impairments, as assessed by the Unified Huntington's Disease Rating Scale Total Functional Capacity (UHDRS TFC ≥ 7) (Huntington Study Group, 1996). Participants with premanifest HD were estimated to be within 15 years to clinical diagnosis (based on Langbehn et al.'s formula: 21.54 + Exp (9.556 – 0.1460 CAG) - age), with an estimated average time to diagnosis of 4.56 years (Langbehn et al., 2004). Premanifest HD participants were on average younger than manifest HD participants, which is expected due to the natural age-associated course of HD. Exclusion criteria for HD participants included comorbid neurological conditions, significant psychiatric disturbances, history of head injury, or history of drug and alcohol abuse. We applied the same exclusion criteria to control participants, and in addition required them to either have no known family history of HD or be genetically confirmed as gene-negative for the HD gene expansion. See Table 1 for cognitive and clinical characteristics of participants.

HD participants were recruited from the Calvary Health Care Bethlehem Hospital and our internal research participant database at Monash University (Clayton, Australia). The Human Research Ethics Committees of Calvary Health Care Bethlehem and Monash University (Australia) approved the study, and all participants provided written informed consent.

Table 1.

Clinical and demographic characteristics of HD (premanifest and manifest) and control participants. Mean ± Standard Deviation (Range).

	Manifest HD (n = 14)	Premanifest HD (n = 16)	Control (n = 30)	*p-value*	*Post-hoc tests*
Sex (M:F)	10:4	7:9	15:15	.28	
Age in years	54.71 ± 7.61 (43-66)	45.38 ± 7.21 (33-56)	50.10 ± 7.55 (38-65)	.005*	Manifest HD > Premanifest HD
Estimated IQ	108.10 ± 9.33 (95-123)	107.04 ± 7.10 (97-126)	109.69 ± 8.93 (91-127)	.59	
CESD-R	7.86 ± 9.40 (0-29)	9.25 ± 11.93 (0-42)	8.33 ± 8.94 (0-37)	.92	
UHDRS TMS	17.31 ± 10.04 (2-40)	1.00 ± 2.14 (0-7)	-	<.001*	Manifest HD > Premanifest HD
UHDRS TFC	10.14 ± 2.14 (7-13)	12.56 ± .89 (10-13)	-	<.001*	Premanifest HD > Manifest HD
DBS	348.86 ± 58.87 (228-485)	319.13 ± 59.02 (247-420)	-	.18	

Note: *P*-Values for age, estimated IQ and CESD-R based on univariate analysis of variance followed by Sidak post hoc tests (p <.05). *P*-Values for UHDRS TMS, UHDRS TFC and DBS based on independent samples t-tests. *P*-Values for sex based on chi-squared tests. Abbreviations: HD = Huntington's disease; Estimated IQ = Estimated Intelligence Quotient measured by the National Adult Reading Test 2nd edition; CESD-R = Centre for Epidemiological Studies Depression Scale - Revised; UHDRS = Unified Huntington's Disease Rating Scale; TMS = Total Motor Score; TFC = Total Functional Capacity; DBS = Disease Burden Score.

Measures

Cognitive and neuropsychiatric characterisation. To estimate participants' premorbid intelligence, we administered the National Adult Reading Test 2nd Edition (NART-2) (Nelson & Willison, 1991). Participants completed the Centre for Epidemiological Studies Depression Scale Revised (CESD-R) (Eaton et al., 2004) as a measure of self-rated depressive symptomology. Possible scores on the CESD-R ranged from 0 to 60, with higher scores indicating increased severity of self-reported depressive symptomology.

Thinking About Life Scale (TALE-R). We used the TALE-R (Bluck & Alea, 2011) to assess three functions of autobiographical memory. The TALE-R is a self-report measure that includes two baseline questions designed to assess how often people think and talk about the past. Following this, 15 items are presented in questionnaire format, addressing three

functions of autobiographical memory: 1) self-continuity (*self*): maintaining a sense of identity over time, 2) social-bonding (*social*): facilitating social bonding and intimacy, 3) directing-behaviour (*directive*): informing current behaviour and guiding future behaviour.

We used the TALE-R with standard administration instructions. First, participants responded to the two baseline questions. Next, participants completed the 15 main items of the TALE-R, which all begin with the statement: "I think back over, or talk about my life or certain periods of my life…", with sample items including "…when I want to try to learn from my past mistakes" and "when I want to develop a closer relationship with someone". All items were rated on five-point Likert scale (1 = Almost Never, 2 = Seldom, 3 = Occasionally, 4 = Often, 5 = Very Frequently). To determine scores for each function, we summed item response scores for that function. The TALE-R has acceptable-good reliability for the self (Cronbach's α = .82), social (Cronbach's α = .80), and directive (Cronbach's α = .80) functions (Bluck & Alea, 2011).

Procedure

Participants were tested during a single session in a quiet testing room. First, participants provided written informed consent and completed a basic demographic questionnaire. We then assessed premorbid intelligence with the NART-2. Next, verbal and written instructions for the TALE-R were provided to participants, and the examiner stayed with the participant to provide clarification if needed while participants filled out the questionnaire. Following completion of the TALE-R, participants completed the CESD-R. We offered reimbursement for the study session to cover travel costs associated with their participation.

Data analysis

IBM-SPSS version 25 was used to analyse the data. Shapiro-Wilk tests of normality were run to assess the suitability of key TALE-R variables for parametric analysis. To

examine overall group differences in the reported frequency of thinking and talking about the past, a 3 (group: manifest HD, premanifest HD, control) x 2 (mode: thinking, talking) mixed-design analysis of variance (ANOVA) was run, followed by Sidak post-hoc tests. Next, group differences in the functions of autobiographical reminiscence were examined using a 3 (group: manifest HD, premanifest HD, control) x 3 (function: social, self, directive) mixed-design ANOVA, with Sidak post-hoc tests. We repeated this analysis with age as a covariate, due to age differences between premanifest HD and manifest HD groups, and report these findings in the Supplemental Materials. We chose to initially examine HD participants as separate groups based on diagnostic status (e.g. manifest HD, premanifest HD), in line with current clinical and diagnostic practice. As we were additionally interested in the continuous nature of changes of autobiographical reminiscence across the spectrum of HD severity, we also conducted a series of Pearson's correlations between autobiographical reminiscence and estimates of disease severity (DBS, TFC, TMS), using a conservative significance threshold of $p = .01$ to control for multiple comparisons.

Results

Frequency of Autobiographical Reminiscence: Thinking vs Talking About the Past

Across groups we found a main effect of mode of reminiscence ($F(1,57) = 9.02$, $p = .004$, $\eta p^2 = .14$), whereby participants reported *thinking* about the past more often than *talking* about the past. A significant group x mode interaction was further evident ($F(2,57) = 3.35$, $p = .04$, $\eta p^2 = .11$). Post-hoc tests indicated that groups differed in their frequency of talking about the past ($F(2,57) = 4.42$, $p = .016$, $\eta p^2 = .13$), with the manifest HD group reporting *talking* about the past less frequently compared to controls ($p = .017$), and a trend towards *talking* about the past less often than premanifest participants ($p = .068$). Premanifest HD and controls did not differ ($p = .99$). In contrast to talking about the past, no group differences were evident regarding *thinking* about the past ($F(2,57) = .008$, $p = .99$, $\eta p^2 < .001$).

Within-group comparisons revealed that the manifest HD group reported thinking about the past more frequently than talking about it (p = .002), whereas no significant differences in mode of reminiscence were observed in either the premanifest group (p = .19) or the controls (p = .58). See Table 2.

Table 2.

Self-reported frequency of thinking and talking about the past on the TALE-R for all participants.

		Manifest HD	Premanifest HD	Control
Think	M (SD)	3.27 (.89)	3.56 (.73)	3.77 (.73)
	Median	3.5 ("Occasionally/Often")	4 ("Often")	4 ("Often")
Talk	M (SD)	2.79 (.97)	3.56 (.73)	3.63 (.96)
	Median	3 ("Occasionally")	4 ("Often")	4 ("Often")

Abbreviations: M = Mean, SD = Standard Deviation

Functions of Autobiographical Reminiscence: Social vs Self vs Directive Functions

A significant main effect of function was observed (F(2,114) = 31.71, p < .001, ηp^2 =.36), with participants reporting using autobiographical reminiscence for *social* and *directive* functions more frequently than for *self* function (all p values <.001). Furthermore, we found no significant differences between the frequency of *social* and *directive* autobiographical reminiscence (p = .68).

We detected a trend towards a main effect of group on the functions of autobiographical reminiscence, which did not reach significance (F(2,57) = 3.01, p = .06, ηp^2 =.10). In contrast, we found a significant group x function interaction (F(4,114) = 3.60, p = .008, ηp^2 =.11). Specifically, post-hoc tests revealed group differences in the social function (F(2,57) = 5.74, p = .005, ηp^2 =.17), with manifest HD participants reporting using social autobiographical reminiscence less than control participants (p = .007). We found no other group differences for the social (ps > .12), the self (p = .12), or the directive functions (p =

.39). Figure 1 displays the self-reported functions of autobiographical reminiscence (self, social, directive) across participant groups.

Looking within each group separately, the manifest HD group trended towards less frequent use of autobiographical reminiscence for the *self* function compared to *directive* function ($p = .07$), with no other significant differences (all other ps >.16). Within the premanifest HD group, participants endorsed using the *self* function of autobiographical reminiscence less frequently than both the social ($p = .01$) and directive ($p = .006$) functions (social vs. directive: $p = .98$). We observed the same pattern within control participants, who reported using autobiographical reminiscence for the *self* function less often relative to the social ($p < .001$) and directive ($p < .001$) functions (social vs. directive: $p = .59$). See Figure 1.

Given the significant age differences between HD participant groups, we repeated the above analyses, including age as a covariate. We observed the same group x function interaction as we observed in the absence of the age covariate (See Supplementary Material).

Association Between Disease Severity Estimates and Autobiographical Reminiscence

To increase statistical power, we investigated the relationship between the frequency and function of autobiographical reminiscence and measures of disease severity in the whole HD group combined (n = 30). We found no significant associations between the frequency of thinking and talking about the past and estimated disease burden (DBS), motor symptom severity (UHDRS TMS) or functional capacity (UHDRS TFC) in the overall HD group.

In terms of the functions of autobiographical reminiscence, an association between higher disease burden and more frequent use of *directive* autobiographical reminiscence was found ($r = .49$, $p = .006$). We found no other associations between disease severity estimates and reminiscence functions using the conservative threshold of $p = .01$.

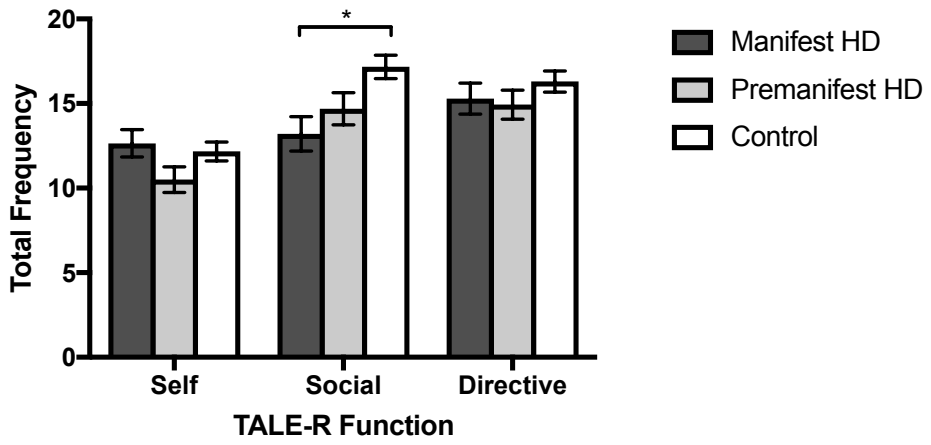

Figure 1. Functions of autobiographical reminiscence (social, self and directive) self-reported by manifest HD, premanifest HD, and control groups on the TALE-R (error bars represent standard error of the mean). *$p < .05$

Discussion

This study is the first to examine the perceived functions of autobiographical memory in HD. The key finding to emerge is the self-reported reduction in using autobiographical reminiscence as a means to engage with others (i.e., social function) in manifest HD. Interestingly, when examining our HD groups separately based on diagnostic status (e.g. manifest HD, premanifest HD), this difference in the use of autobiographical reminiscence was observed exclusively for the social function. Social aspects of autobiographical memory are reported as being the most frequently utilised function across adulthood in healthy populations allowing individuals to reflect upon or share significant personal and collective narratives with others (Harris et al., 2014). Our findings suggest that in parallel with a diminished capacity for autobiographical recollection (Carmichael, Irish, Glikmann-Johnston, Singh, & Stout, 2019), people with manifest HD may also be foregoing the benefits of interpersonal bonding that shared reminiscence fosters (Alea & Bluck, 2003). As such, our

research provides initial evidence for a perceived disruption in the function of autobiographical memory in HD.

The observation of a disruption to the perceived social function of autobiographical reminiscence in manifest HD resonates with the well-documented impairments in social cognition in HD (Eddy, Parkinson, & Rickards, 2016). Impairments in both emotion recognition (Kempnich et al., 2018; Kordsachia, Labuschagne, & Stout, 2017) and theory of mind (Eddy, Sira Mahalingappa, & Rickards, 2012) have been reported in HD, which have been linked to social dysfunction. Subsequently, we hypothesise that these impairments affect the ability or desire to engage in socially-oriented autobiographical reminiscence. Furthermore, as apathy and reduced initiation are interrelated neuropsychiatric features of HD (Paulsen et al., 2001), this may further alter the likelihood of people with HD seeking out social situations to engage in autobiographical reminiscence. Communication difficulties are frequently reported in manifest HD (Chenery, Copland, & Murdoch, 2002; Jona et al., 2017), including reduced initiation of communication and self-reported reductions in the number of opportunities available to have meaningful social interactions with others (Hartelius, Jonsson, Rickeberg, & Laakso, 2010). As such, we cannot rule out that reduced social reminiscence seen in manifest HD participants may be due to communication dysfunction more broadly. Future studies examining the interplay between social cognition, communication, and reminiscence in HD may help to better understand the mechanisms underlying reported reductions in social reminiscence.

Within-group comparisons provided preliminary evidence in favour of a gradient of changes in the function of autobiographical reminiscence from premanifest to manifest HD. Healthy controls and premanifest HD endorsed using autobiographical reminiscence more frequently for social and directive functions rather than for self-functions. This complements the well-established finding of a prospective bias during spontaneous reflection and the

tendency towards thinking about others rather than the self with increasing age (Irish, Goldberg, Alaeddin, O'Callaghan, & Andrews-Hanna, 2018). In contrast, manifest HD participants did not endorse the preferential use of any type of function during autobiographical reminiscence. Looking across the entire HD cohort, we found that more severe *estimated* disease burden was associated with an increase in the perceived use of reminiscence for directive purposes. It is, however, important to note that we did not detect relationships with objective measures of HD severity gained from clinical examination (e.g., TMS, TFC). This incongruence may be accounted for by findings that DBS accounts for only 60% of the variability of the age of clinically manifest motor symptom onset in HD (Gusella, MacDonald, & Lee, 2014), and thus serves as a useful but not precise estimate of disease severity in HD. Given the mixed-findings for the relation between disease severity and directive reminiscence in HD, and the lack of findings yielded from our group comparisons, more work is needed to better understand how the perceived utility of directive-reminiscence may change over the HD disease course. Furthermore, given the close correspondence between autobiographical memory retrieval and the self (Conway, Singer & Tagini, 2004), it remains unclear how changes in autobiographical reminiscence affect a sense of self-continuity in HD. A key role has been proposed for semantic autobiographical memories in supporting self-continuity over time (Prebble et al., 2013). Given our previous finding of relatively intact semantic autobiographical retrieval in HD (see Carmichael et al., 2019), we suggest that HD participants likely draw upon personal semantics (e.g. general facts and information) to ground the self (see also Strikwerda-Brown et al., 2019), however empirical studies are required to formally test this hypothesis.

This study provides preliminary insights into how the perceived function of autobiographical memory changes in the premanifest and manifest stages of HD. A number of methodological issues, however, warrant consideration, most notably our relatively small

sample size, which may have limited our power to detect group differences on the TALE-R. We further note the inherent limitations with using any self-report measure in a clinical population characterised by varying degrees of cognitive impairment. Studying people with HD who are at the premanifest stage or early in the course of the disease goes some way towards mitigating the risk of faulty self-report data due to against the potential loss of insight in participants. We note, however, that it will be important to develop objective or verifiable measures of the constructs of interest. For example, future studies corroborating social aspects of reminiscence with family members or caregivers may go some way to verifying the relatively more limited use of social aspects of reminiscence in HD. Furthermore, to better understand the impact of autobiographical impairments in HD on the self, future work should examine themes related to the self across past and future narratives (Grilli et al., 2018; Strikwerda-Brown, Grilli, Andrews-Hanna, & Irish, 2019). Similarly, assessing the integrity of future thinking or prospection in HD will help us better understand the relative relationship between autobiographical reminiscence and the directive function in HD. The current work nevertheless provides important initial insights regarding how subjective aspects of autobiographical memory may change across the HD disease trajectory and suggests that elements of reminiscence therapy encouraging socially-oriented reminiscence (Woods et al., 2018) may prove particularly useful in HD.

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Supplemental Materials

Frequency and function of autobiographical reminiscence

A 3 (group: control, premanifest HD, manifest HD) x 2 (mode: thinking, talking) mixed-design analysis of covariance (ANCOVA) controlling for age did not reveal a main effect of mode of reminiscence ($F(1,56) = .78$, $p = .38$, $\eta p^2 = .014$), however the mode x group interaction remained significant ($F(2,56) = 3.31$, $p = .04$, $\eta p^2 = .11$). When age was controlled for, compared to manifest HD participants, both controls ($p = .01$) and premanifest HD ($p = .04$) reported talking about the past more frequently. No difference between premanifest and controls was detected ($p = .01$). Again, no group differences were detected for frequency of thinking about the past, $F(2,56) = .008$, $p = .99$, $\eta p^2 < .001$.

For the functions of autobiographical reminiscence, a 3 (group: control, premanifest HD, manifest HD) x 3 (function: self, social, directive) mixed-design ANCOVA did not reveal an overall effect of function *(*$F(2,112) = 1.56$, $p = .21$, $\eta p^2 = .03$), but showed the same group x function interaction as before ($F(4,112) = 4.21$, $p = .003$, $\eta p^2 = .13$). Post-hoc tests revealed a significant group difference in the social function ($F(2,57) = 5.74$, $p = .005$, $\eta p^2 = .17$), driven by manifest HD reporting using the social function of autobiographical reminiscence less than controls ($p = .002$). Finally, we did not detect a main effect of group but again, this approached significance ($F(2,56) = 2.92$, $p = .06$, $\eta p^2 = .09$).

CHAPTER 6: GENERAL DISCUSSION

6.1 Overview of Main Findings and Contribution to the Literature

Autobiographical memory is an ecologically relevant form of memory that encompasses the ability to encode and retrieve personally-experienced self-referential events from across the lifespan. From a functional perspective, autobiographical memory has important implications for a person's sense of self, social-connectedness, and ability to imagine the future. This thesis is the first body of work to examine autobiographical memory in HD, a neurodegenerative disorder characterised by early motor, cognitive and psychiatric changes. We examined '*what'* people living with HD can remember from their lives, '*how'* autobiographical memory dysfunction relates to the neuropathology associated with HD, and '*why'* people with HD use their autobiographical memories in their daily lives. By integrating cognitive, neuroimaging and functional methods in this thesis, we provide seminal insights into autobiographical memory function and utility in HD, and further our understanding of the cognitive phenotype in late premanifest and early manifest HD.

Collectively, the experimental chapters of this thesis (Chapters 3-5) have allowed us to categorise autobiographical memory functioning in HD and identify pervasive impairments in episodic autobiographical memory (personal memories from a specific time and place), broadly intact semantic memory (knowledge and facts accumulated from across the lifespan not bound to a specific time and place), and provide evidence for an association between striatal degeneration and autobiographical impairments. In addition, we have contributed to understanding of the functional impact of autobiographical dysfunction in HD, finding a reduction in the self-reported function of autobiographical memory to facilitate social bonding and connectedness with others in the manifest stage of HD. The key findings that have arisen from this thesis are summarised below.

The first aim of this thesis, detailed in Chapter 3, was to determine whether episodic memory deficits in HD extend to the domain of personally-relevant retrieval of past

memories. We investigated autobiographical memory function using the AI, a semi-structured interview that examines the ability to recall contextually rich life events from five life epochs ranging from childhood to the last 12-months. The AI employs a fine-grained scoring method, enabling quantification of the number of episodic autobiographical details a person can retrieve for a specific event, reflecting an overall sense of re-experiencing. Furthermore, the AI can be used to characterise the non-episodic details associated with an autobiographical narrative, including semantic information, repetitions and metacognitive statements. Using the AI in HD, we found pervasive episodic autobiographical memory impairments, which affected the retrieval of both remote and recent events to similar degrees. We further detected similar levels of impairment across all types of episodic detail (i.e., event, spatiotemporal, perceptual, emotion/thought), suggesting that overall impairments were relatively general, and not driven by recall difficulties for only a specific subcategory of detail. At a group level, the degree of episodic autobiographical memory impairments was similar for late premanifest and early manifest HD groups. Nonetheless, when looking across the combined group of premanifest and early manifest HD, we found that measures of disease severity (e.g., TMS, TFC) were associated with more pronounced autobiographical memory impairments. This suggests that there may be subtle changes in autobiographical memory in HD between the late premanifest and manifest stages of HD that we did not detect in our between-group analysis. Further, we detected possible evidence of compensation in the premanifest HD group under the probed condition, whereby premanifest HD participants populated their impoverished episodic narratives with more non-episodic autobiographical details (e.g., repetitions, semantic details, metacognitive statements), a finding not present in manifest HD. As the first study of autobiographical memory function in HD, our findings in Chapter 3 provide a significant contribution to the memory literature in HD, extending our

understanding of the memory phenotype of HD to an ecologically relevant domain by thoroughly describing autobiographical memory function.

In Chapter 4 we addressed the second aim of this thesis, which was to determine the association between the hallmark striatal degeneration that invariably occurs in HD in relation to autobiographical memory capability. We used manual MRI volumetry to investigate the association of autobiographical memory to striatal regions (i.e., the caudate nucleus and putamen) and hippocampal volumes in HD. We found that striatal atrophy, in particular caudate volume, was associated with free recall of autobiographical memory. Given the position of the caudate as a key part of the fronto-striatal systems, which are important for autobiographical retrieval operations including strategic search, verification, monitoring and cognitive control, this finding adds to evidence that striatal degeneration is associated with impaired autobiographical memory. Further, both hippocampal volume and striatal volumes were associated with probed autobiographical performance in HD. This finding is consistent with previous neuroimaging studies showing activity in the hippocampus during autobiographical memory construction and elaboration (McCormick et al., 2013), and also compliments recent work highlighting that the hippocampus and striatum work in cooperation to facilitate episodic memory (Ben-Yakov & Dudai, 2011; Sadeh et al., 2011). These findings together provide further support to the emerging association between the striatum and the ability to retrieve personally-salient autobiographical memories. Overall, our findings have importance beyond HD, as they suggest that other clinical profiles characterised by subcortical dysfunction and relatively intact cortical regions (e.g., Parkinson's disease) may also be susceptible to disruptions in retrieval of autobiographical details from across one's lifetime.

Moving beyond the characterisation of autobiographical memory dysfunction and its neural correlates in Chapters 3 and 4, Chapter 5 aimed to determine *how* autobiographical

memory is used in autobiographical reminiscence in HD, which was investigated using self-report measures. According to other published work, autobiographical memory is posited to serve self, social and directive functions (Bluck et al., 2005; Prebble et al., 2013), thought to be important to overall quality of life, yet the self-reported function of autobiographical reminiscence has not been extensively examined in neurodegenerative disorders. Thus, we aimed to assess the self-reported frequency and function of autobiographical reminiscence in HD by examining the perceived uses of autobiographical reminiscing using the TALE-R, a short self-report measure. People living with manifest HD reported *talking* less frequently about the past compared to controls. In contrast, all groups reported similar levels of thinking about the past. This finding demonstrates a discrepancy in manifest HD in terms of how people engage in internal versus external reminiscence. We hypothesise that this reduction in external relative to internal reminiscence may be either due to documented impairments in social cognition in HD (Snowden et al., 2003) or communication difficulties (Hartelius et al., 2010). HD participants further reported using their autobiographical memories for social functions less frequently compared to controls. These findings suggest that people living with manifest HD perceive themselves as using their autobiographical memory less for social reasons and talking about their memories in general less than their age-matched peers. This finding is the first, to our knowledge, to assess the self-reported uses of memory in HD, and it provides a unique contribution to the field by highlighting that people in the manifest stage of HD exhibit subtle reductions in the way they use their memory for social connectedness.

Taken together, our findings give the first detailed picture of how autobiographical memory is affected across the late premanifest and early manifest stages of HD. To summarise, compared to healthy controls, during the premanifest stage of HD, fewer specific episodic details are retrieved about particular events, and instead, narratives tend to be supplemented with other non-episodic information, such as general facts, repetitions, and

metacognitive commentary. We speculate that this may be compensatory, whereby semantic information stays relatively intact with disease progression and thus can be used to 'fill-in' the gaps when details of an autobiographical narrative cannot be accessed, which is a trend also found in healthy ageing as we rely more on semantic information to populate narratives (Levine et al., 2002). In manifest HD, we observed the same pattern of impaired retrieval of episodic autobiographical details, however, we *did not* observe the same compensatory increase in semantic details which we observed premanifest HD. This means that people living with manifest HD tend to recall shorter, more detail-poor narratives compared to people earlier in disease progression. Importantly, there further appears to be a subtle, but potentially meaningful difference, in the way people with manifest HD perceive the function of the memories, self-reporting lower uses of social reminiscence compared to premanifest HD and controls. Overall, our findings provide novel insights into autobiographical memory in HD, demonstrating that the integrity of autobiographical memory systems begins to deteriorate in the late premanifest stage of HD, but that the self-reported impact of this deterioration is not realised (relative to healthy peers) until the manifest stage of HD. We next discuss the implication of these findings both for the HD literature, and for the autobiographical memory literature.

6.2 General Discussion and Implications

6.2.1 Implications for memory in HD. Episodic memory impairments have been a recognised feature of HD for the past 3-4 decades. Early research in HD reported impairments in the free-recall of episodic information, with relatively spared recognition (Butters et al., 1985), whereby memory problems in HD were considered to primarily be executively driven retrieval deficits. Our understanding of the nature of episodic memory impairments in HD has grown rapidly since early studies, largely thanks to large scale, longitudinal observational studies (e.g. Solomon et al., 2007; Stout et al., 2011) and meta-

analyses (e.g., Montoya et al., 2006), which have reported that both recall and recognition are impaired in the early manifest and late premanifest stages of HD, and that subtle impairments are detectable even further away from diagnosis in premanifest HD (e.g. 9-15 years) with adequate sample sizes (Stout et al., 2011). Although these findings from classic word-list and story learning tasks provide the foundation of our knowledge about episodic memory in HD, they lack ecological relevance to how we use memory in everyday way. By adding information about an additional aspect of memory function, via examining autobiographical memory, we have evaluated a new and valuable dimension of memory function that has importance for sense of self and identity over time (Bluck et al., 2005). As such, one of the first important findings from our study was identifying impairments in both free and probed autobiographical memory in HD that extend previous work into a more ecologically relevant context by demonstrating that even with probing and increased retrieval support, people in the late premanifest and early manifest stages of HD cannot access the same number of contextually-rich details about a past experience as their healthy peers.

From a cognitive perspective, another major contribution of our study was advancing our knowledge of remote memory in manifest HD. Previous research studied remote memory in HD using experimental tasks that examined the ability to recall semantic information from different decades, including well-known world events and famous faces (Albert et al., 1981; Beatty et al., 1988). These studies provided valuable contributions to our understanding of remote memories, but were limited by relying on the assumption that people learned/encoded information in a specific decade (e.g. the decade when a renowned public event occurred, or the decade a particular public figure was popular), where in practice, this may not be the case and a person may have learned the information (e.g., public event, famous face) much later in their lives (Albert et al., 1981; Beatty et al., 1988). Our study overcame this limitation using the AI, requiring participants to retrieve accounts of autobiographical events from a specific

time and place within a certain epoch (e.g. childhood, teenage years, etc.). Consistent with the beforementioned earlier studies of remote memory in manifest HD, we did not find any significant differences in the number of episodic details retrieved from remote or recent memories in our participants. As well as building on previous knowledge in manifest HD to show that the retrieval of remote and recent memories are impaired to a similar degree, our study is also the first, to our knowledge, to characterise remote memory in *premanifest* HD. Similar to our manifest HD group, we found that both remote memories and recent memories showed similar levels of impairment. Taken together, the flat gradient across epochs suggests that autobiographical memories are suspectable to disruption that are *encoded* both before (i.e., childhood) and after (i.e., within the last year) HD-related pathology is detectable. This suggests a pattern of both anterograde and retrograde memory impairment present in late premanifest and early manifest HD. Understanding the nature of remote memory impairments in people genetically confirmed to have the HD CAG expansion who are further from diagnosis, and thus have less notable HD-related brain pathology, will be an interesting future direction to further understand the integrity of remote memory across the spectrum of disease burden in HD.

Turning the attention to our neuroimaging findings, this thesis has increased our understanding of the cognitive correlates of striatal degeneration in HD. Whereas subcortical degeneration in HD was traditionally viewed as primarily affecting motor sequencing and implicit memory (Heindel et al., 1988; Heindel et al., 1989; Walker, 2007), our findings support more recent evidence that cognition is also affected by striatal degeneration. Although the majority of work comparing striatal degeneration to cognition tends to focus on *working memory* (e.g. Wolf et al., 2009), there is a small but important body of literature that has reported subtle relationships between striatal atrophy and impairments on word-list learning tasks in HD (Campodonico et al., 1998; Harrington et al., 2014; Solomon et al.,

2007; Starkstein et al., 1992). We have extended these findings to show that striatal atrophy, in particular degeneration of the caudate nucleus, is also associated with impaired ability to freely recall autobiographical details from across the lifespan, and that both caudate and putamen volumes are associated with recalling autobiographical memories with increased retrieval support (e.g. when probed). In addition to finding that *striatal atrophy* was associated with cognitive impairments in our sample, we also found that the hippocampus was associated with the ability to elaborate on autobiographical events when prompted or probed to give more information. Thus, our findings are consistent with the possibility that the striatum may work cooperatively with the hippocampus (and likely also with other brain structures) to support successful memory operations (Ben-Yakov & Dudai, 2011; Sadeh et al., 2011).

In addition to advancing our understanding of autobiographical memory from a cognitive and neural perspective in this thesis, in Chapter 5 we have provided initial insights on the potential psychosocial impact of autobiographical memory impairments in HD. Specifically, this was the first published research, to our knowledge, to examine the perceived functions of autobiographical memory in HD. We found that people with manifest HD self-reported a reduction in using autobiographical reminiscence as a means to engage with others (i.e., social function). This is a particularly interesting finding, as social aspects of autobiographical memory are reported as being the most frequently utilised function across adulthood in healthy populations allowing individuals to reflect upon or share significant personal or collective narratives with others (Harris et al., 2014). Our findings suggest that in parallel with a diminished capacity for autobiographical recollection as demonstrated in Chapter 3, people with manifest HD may also be foregoing the benefits of interpersonal bonding that shared reminiscence fosters (Alea & Bluck, 2003). Based on this, we suggest that elements of reminiscence therapy that encourage socially-oriented reminiscence (Woods

et al., 2018) may prove particularly useful in HD as routine psychosocial interventions remain limited in HD (Walker, 2007). Although evidence for the efficacy of reminiscence-based therapies is often overshadowed by early inconclusive findings, which has typically been attributed to methodological issues and small sample sizes (O'Philbin et al., 2018), promising evidence for the potential benefits of these therapies for cognition, mood, and quality of life has emerged in recent years as methodological issues in approaches have been amended (e.g., O'Philbin et al., 2018). Thus, we suggest that autobiographical memory or reminiscence-based interventions may be useful to consider evaluating in HD.

6.2.2 Implications for autobiographical memory. There are a number of findings from this thesis that contribute to the fundamental understanding of autobiographical memory. The first is that autobiographical memory may be implemented partially within subcortical brain structures. This is the first study to show robust autobiographical memory deficits in a neurodegenerative disorder characterised primarily by subcortical degeneration rather than cortical degeneration that dominates other more common neurodegenerative disorders which have extensively featured in the autobiographical memory literature. Autobiographical memory impairments are well established as a pervasive feature in many cortically-based neurodegenerative disorders including Alzheimer's disease (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012; Irish et al., 2011), fronto-temporal dementia (Irish et al., 2014; Piolino et al., 2003), and posterior cortical atrophy (Ahmed et al., 2018). Interestingly, previous research in autobiographical memory research in Parkinson's disease (e.g. Smith, Souchay, & Conway, 2010), which like HD is characterised by subcortical dysfunction, has yielded mixed results regarding whether autobiographical memory is or is not impaired. We speculate that this may be due to methodological differences in terms of the behavioural task used in these studies. That is, Parkinson's disease studies have employed the Autobiographical Fluency task (Dritschel et al., 1992), which

emphasises the quantity of different *events* that can be recalled rather than the quantity of autobiographical *details* that can be retrieved about a specific event. In other words, the use of fluency-based autobiographical memory tasks (i.e., the Autobiographical Fluency Task) does not enrich our understanding of the contextually-rich details that can be brought to mind about a past event. As such, future work investigating the integrity of autobiographical memory in brain disorders such as Parkinson's disease utilising fine-grained scoring protocols such as the AI will be an important avenue of research to further understand the cognitive phenotype in subcortical dementia due to the mounting evidence that suggests that subcortical regions may play an important role in mediating successful episodic encoding and retrieval (Ben-Yakov & Dudai, 2011; Sadeh et al., 2011).

Beyond finding autobiographical deficits in HD on our behavioural task in Chapter 3, we were able to investigate the specific associations between striatal degeneration and autobiographical memory performance in Chapter 4, providing evidence for a relationship between the striatum (and particularly the caudate nucleus) and autobiographical retrieval. The core network of structures typically purported to support autobiographical retrieval includes medial temporal, frontal, lateral temporal, sensory association, and posterior parietal regions (Cabeza & St Jacques, 2007; Svoboda et al., 2006). In addition, secondary and tertiary regions are also described in the literature, including the amygdala and thalamus. Our finding of associations between striatal atrophy and impaired autobiographical memory are consistent with recent findings from Esopenko and Levine (2017), as well as from the cognitive neuroscience literature, which argue that the striatum plays a role in mediating prefrontal operations that support autobiographical memory, and which work cooperatively with the hippocampus to facilitate episodic encoding and retrieval (Murty, DuBrow, & Davachi, 2015; Sadeh et al., 2011).

6.3 Methodological Considerations and Future Directions

We gained a number of methodological insights from this thesis, which will be important to consider in future research. The first methodological limitation from this body of work is related to the objective scoring method utilised in our study. Despite the rigorous text segmentation system utilised to quantify the type of autobiographical details participants retrieved using the AI (Levine et al., 2002), inherent limitations have been highlighted in recent research (e.g. Strikwerda-Brown et al., 2018), and should be considered when interpreting results and planning future research. One limitation when using the AI scoring system relates to the accuracy by which the AI measures the integrity of *semantic* retrieval. Specifically, the AI purports to capture the naturalistic manner in which we recall both episodic and non-episodic elements, including semantic knowledge, when targeting retrieval of autobiographical events from a specific time and place. The standard scoring protocol of the AI (Levine et al., 2002), however, which we utilised throughout the thesis project, combines both personal semantic information, i.e*., self-knowledge*, and general knowledge, i.e., *facts about the world*, into a 'semantic composite'. Because the personal and world-related knowledge is combined into a single index, it is therefore impossible to specifically quantify the relative integrity of autobiographical semantic memory. Since our study was completed, a new scoring protocol has been proposed by Strikwerda-Brown and colleagues (2018) to better discriminate the types of *external details* retrieved in the AI, importantly, including classifying external information as personal semantic (personal self-knowledge) or general semantic (general knowledge about the world). This new scoring protocol acknowledges that semantic information retrieval may be autobiographical (e.g. "I was born in Benalla") or general in nature (e.g., "Melbourne is the capital of Victoria"). Incorporating this adapted scoring protocol in future research that utilises the AI will allow more in-depth

understanding of the integrity of semantic autobiographical memory, in addition to the already thorough classification the AI provides of episodic autobiographical memory.

Another methodological consideration to emerge from our study relates to practical limitations in the number of brain regions we were able to measure using the image analysis techniques we employed. The manual segmentation of grey matter structures, reported in Chapter 4, allowed precise delineation of specific brain regions (i.e., caudate nucleus, putamen, and hippocampus), however, because such approaches are so time consuming, it naturally limited the number of structures we could examine (Schoemaker et al., 2016). As such, this meant that we were unable to examine the broader neural substrates of autobiographical memory, known to encompass a complex network of prefrontal, medial temporal and posterior regions (Cabeza & St Jacques, 2007; Svoboda et al., 2006). Examining the relative contribution of prefrontal and striatal regions will be an important future direction. As subtle prefrontal volume loss has been reported in the premanifest stage of HD (Gómez-Ansón et al., 2009), typically ascribed to a loss in frontal white matter (Montoya, Price, Menear, & Lepage, 2006), comparing the functional connectivity of these structures, as well as other key nodes of the autobiographical network, will better help to understand the neural substrates of autobiographical memory more broadly. To achieve this, utilising automated techniques such as VBM or DTI will be needed to elucidate the neural network underpinning autobiographical memory in HD in a more comprehensive and time-efficient manner.

As with many studies in relatively rare neurodegenerative diseases, the sample size we were able to study was relatively small, and therefore limits the generalisability of our findings. The incidence of HD is estimated to be 5.63 per 100,000 in Australia (Rawlins et al., 2016) which limited the pool of potential research participants available for recruitment. Furthermore, many people in the late-premanifest and early-manifest stages of HD may still

be involved in employment or volunteer work, restricting their availability to engage in relatively demanding testing procedures. Studies with larger sample sizes, particularly within the premanifest group, would allow more careful examination of *when* in the disease process autobiographical impairments begin in relation to the pathological progression of HD, which would enhance understanding of the continuum of autobiographical changes that occur during the course of HD.

Our findings of impaired episodic autobiographical memory provide rationale for the investigation of future thinking in HD as the neural systems supporting episodic memory have also been implicated in the ability to imagine or simulate events that might occur in the future (Addis et al., 2007). Functionally, the ability to prospect into the future has important implications for decision making, emotion regulation, intention formation, planning and a person's sense of self across time (Schacter, Benoit, & Szpunar, 2017). The link between episodic remembering and episodic future thought is sometimes referred to as the constructive episodic simulation hypothesis, which suggests that episodic memory supports future simulation of events by allowing a person to retrieve and recombine elements of past experiences into novel representations of events that could occur in the future (Schacter & Addis, 2007). In contrast, a more recent semantic scaffolding hypothesis posits that semantic memories provide a framework that guides future thinking (Irish & Piolino, 2016; Schacter et al., 2017). As such, understanding the integrity of future thinking in HD will be important to better understand the potential impact of cognition on various aspects of functioning. Findings of future work in this area will be particularly interesting in HD considering the relatively intact profile of semantic memory found in the current body of work, in addition to the pervasive patterns of episodic autobiographical memory impairments. As such, it would be expected that future prospection would be possible in HD, but the quality of detail in prospective future-thinking accounts may be impaired (consistent with episodic

autobiographical memory impairments) as seen in other neurodegenerative disorders (Irish & Piolino, 2016).

6.4 Conclusions

The overall aim of the body of research presented in this thesis was to describe and explain autobiographical memory in HD, and to contextualise this new understanding of autobiographical memory within the broader picture of how memory is affected by HD. By combining performance-based cognitive, neuroimaging, and self-report approaches, we extended the understanding of episodic memory impairments in HD, which have been mainly limited to classic story and word-list learning tasks, to the ecologically-relevant and personally meaningful domain of autobiographical memory. Our most novel finding from this research was that episodic autobiographical memory impairments occur in the late pre-manifest and early manifest stages of HD for both recent and remote memories, and that these impairments are related to caudate atrophy. Additionally, we report a subtle reduction in the self-reported use of autobiographical memory for social purposes in manifest HD. Further understanding the link between HD, autobiographical memory and interpersonal functioning will enable better understanding, and potentially also therapeutic approaches that will foster the quality of life of people living with HD. In sum, this research has advanced our understanding of *how* and *why* people living with HD use their autobiographical memories and we hope that these findings will inform the development of psychosocial interventions to decrease burden, improve well-being, and increase social connectedness for people living with HD.

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APPENDIX

Appendix A: Pervasive autobiographical memory impairments in Huntington's disease

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Pervasive autobiographical memory impairments in Huntington's disease

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ABSTRACT

Autobiographical memory dysfunction is a pervasive feature of neurodegenerative disorders, but less is known about the integrity of autobiographical memory in Huntington's disease (HD). Deficits in anterograde verbal episodic memory on traditional neuropsychological tests have been detected in HD, however, whether personally-relevant autobiographical retrieval is also affected is unknown. We examined autobiographical memory performance in 26 participants genetically confirmed to have HD who were in the peri-manifest stage of the disease (including 12 in the late premanifest stage and 14 who were early diagnosed), and 24 matched controls using the Autobiographical Interview (AI), a semi-structured interview assessing retrieval of autobiographical details from discrete epochs across the lifetime. Relative to controls, people with HD exhibited global episodic autobiographical memory impairments, regardless of recency or remoteness of the memory being retrieved. While specific cues bolstered the retrieval of episodic (internal) details in HD participants, their performance remained significantly below that of controls. Moreover, following probing, people with HD retrieved more extraneous (external) details not directly related to the autobiographical event they originally retrieved, including semantic details, repetitions, and metacognitive statements. Our results reveal marked autobiographical memory dysfunction in HD, not directly attributable to strategic retrieval deficits, and suggest that autobiographical memory impairment may represent an overlooked feature of the cognitive phenotype of HD.

Huntington's disease (HD) is an inherited neurodegenerative disorder characterised by progressive cognitive, neuropsychiatric and motor symptoms. The unequivocal presence of the characteristic motor signs of HD (e.g., chorea) defines the current diagnostic basis for when HD is considered manifest; however, cognitive decline is detectable at least ten years prior to this diagnostic threshold (Paulsen et al., 2008). Deterioration of executive function, emotion recognition, and anterograde episodic memory are among the known early cognitive deficits in HD, and are detectable in the years leading up to, as well as after diagnosis (Coppen et al., 2018; Kordsachia et al., 2017; Stout et al., 2011).

Episodic memory dysfunction has been documented on standard neuropsychological tests of story and word-list recall in both premanifest and diagnosed HD (Montoya et al., 2006; Solomon et al., 2007). Impairments in semantic memory (facts and knowledge) have also been reported in HD, however, these difficulties are typically attributed to initiation and retrieval dysfunction, rather than a breakdown in semantic knowledge stores per se, which remain relatively preserved (Hodges et al., 1990; Rosser and Hodges, 1994). Limited research has endeavoured to investigate whether there is a differential impairment in recent or remote memory in HD. The few published studies in this area have used testing protocols primarily taxing semantic memory via public event questionnaires (e.g. well-known events that occurred in different decades) or famous face recognition tasks (faces of public figures who were famous in different decades). These studies reveal disruption of non-personal remote and recent memory in people with HD (Albert et al., 1981; Beatty et al., 1988). In contrast, the status of personally-relevant recent and remote memories remains unclear as no study to date has investigated the integrity of autobiographical memory in HD.

Autobiographical memory is our memory for personally experienced events and personal knowledge amassed across the lifespan (Conway et al., 2004), and involves both episodic and semantic components (Levine et al., 2002). The capacity to remember information about one's own life is linked to both wellbeing and sense of identity (Addis and Tippett, 2004; Jetten et al., 2010; Prebble et al., 2013).

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Episodic autobiographical memories are recollections of personally experienced events and occurrences from a specific time and place from our lives that leave robust memory traces over time (Moscovitch et al., 2016). Such memories create a feeling of re-experiencing when recollected and include perceptual information, spatiotemporal context, and emotional content (Irish et al., 2011a; Levine et al., 2002). Mounting evidence reveals that enmeshed within the autobiographical narrative are semantic elements, comprising extended events, personal facts and knowledge from our lives (Strikwerda-Brown et al., 2018). Previous studies have documented a shift from episodic to semantic styles of retrieval with increasing age, with older adults displaying reduced episodic details, offset by an increase in semantic information (Levine et al., 2002), a process that likely serves important adaptive functions.

Autobiographical memory retrieval is particularly vulnerable to disruption in neurodegenerative disorders, including Alzheimer's disease (Barnabe et al., 2012; Irish et al., 2011a) and frontotemporal dementia (Irish et al., 2014, 2011a; Piolino et al., 2003). Such deficits reflect the widespread degeneration of key nodes within the brain's core memory network including the medial temporal lobes, medial prefrontal cortex, and posterior parietal circuitry (Irish et al., 2014; McKinnon et al., 2008). Compared to more cortically-affected neurodegenerative diseases, autobiographical memory research in neurodegenerative disorders with considerable subcortical pathology has been limited. The few studies in Parkinson's disease have found that free-recall of autobiographical memories is reduced (Smith et al., 2010), but that performance improves to a level equivalent to controls when cues are provided (Souchay and Smith, 2013). HD is characterised by striking disruption to fronto-striatal circuitry and pronounced striatal atrophy detectable up to 20 years before clinical diagnosis (Tabrizi et al., 2013), which progresses to more widespread global atrophy to both grey and white matter (Vonsattel et al., 2011), including hippocampal atrophy (Douaud et al., 2006; Rosas et al., 2003; van den Bogaard et al., 2011). Evidence regarding hippocampal integrity in premanifest HD has been mixed, with some studies detecting no differences between premanifest HD and controls (Possin et al., 2017), while others report subtle volume reductions in people with late premanifest HD (Faria et al., 2016; van den Bogaard et al., 2011).

The aim of this study was to determine whether episodic memory deficits in HD extend to the domain of personally-relevant retrieval of the past using a widely used measure of autobiographical memory, the Autobiographical Interview (AI; Levine et al., 2002). We further examined whether autobiographical memory impairments in HD affect recent and remote memory recall comparably, and whether impairments manifest in a graded manner across time periods. In addition, we sought to establish how the retrieval of specific types of contextual details is altered in HD using a fine-grained scoring method. Finally, to understand the potential mechanisms driving autobiographical memory impairments in HD, we examined the relationship between autobiographical memory and traditional neuropsychological tasks. Based on known episodic memory deficits in HD from previous studies, we predicted that people with the huntingtin gene expansion, regardless of whether they were in the early manifest or late premanifest phase, would exhibit impaired episodic autobiographical memory retrieval compared to healthy age-matched control participants, with autobiographical memory ability varying in relation to the severity of HD.

1. Methods

1.1. Participants

We recruited 26 participants genetically confirmed to have the HD gene in the peri-manifest stage of the disease, including 14 participants with early stage [or manifest] HD and 12 participants who were estimated to be at the late premanifest stage of HD. Premanifest HD participants in our sample were estimated, based on their ages and CAG repeat expansion sizes, to be within 10 years to clinical diagnosis with an estimated average years to diagnosis of 3.42 years as per Langbehn et al. (2010) formula, and had a Disease Burden Score (DBS) > 250 (DBS formula: (CAG repeat length – 35.5)*age; Penney et al., 1997). Further, all HD participants had a Total Functional Capacity ≥ 7 (Huntington Study Group, 1996), suggesting minimal to moderate clinical impairments in the overall HD sample. For characterisation of disease progression, all participants with HD were evaluated using the motor and functional components of the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996). A higher UHDRS Total Motor Score indicates more severe motor signs, while higher scores on the UHDRS Total Functional Capacity scale indicate less functional impairment on basic activities of daily living.

As expected, premanifest HD participants in our sample had significantly lower UHDRS Total Motor Scores compared to manifest HD participants ($p < 0.001$; premanifest HD: M = 1.17, SD = 2.37; manifest HD: M = 17.31, SD = 10.04) and had a significantly higher UHDRS Total Functional Capacity ($p < 0.001$; premanifest: M = 12.83, SD = 0.39; manifest: M = 10.14, SD = 2.14). The HD subgroups did not differ significantly in terms of their DBS, suggesting comparative estimated disease burden between groups ($p = 0.24$; premanifest: M = 321.96, SD = 53.87; manifest: M = 348.86, SD = 58.87).

For comparison, we recruited 24 healthy control participants matched to the overall HD cohort of participants for age, sex, and estimated premorbid intelligence. For recruitment, we identified participants from the Statewide Progressive Neurological Disease Service at Calvary Health Care Bethlehem and from our internal research volunteer database at Monash University (Clayton, Australia). Exclusion criteria for HD participants included a diagnosis of a neurological disorder other than HD, diagnosis of a severe psychiatric condition, alcohol and other drug abuse, and limited English proficiency (because of language demands of the autobiographical memory task). The same exclusion criteria applied to control participants, with additional inclusion criteria of having no family history of HD or confirmation as gene-negative.

Ethical approval was obtained from the Monash University Human Research Ethics Committee and Calvary Health Care Bethlehem Research Ethics Committee, and written informed consent was obtained from each participant. Reimbursement was offered to cover travel costs and time for all participants.

1.2. Procedure

Participants attended a single session for testing by an examiner (AMC), which took approximately 90 min. Testing included measures for characterisation of cognitive functioning, as well as autobiographical memory.

1.2.1. Cognitive characterisation

To estimate intellectual ability and cognition, we used traditional neuropsychological tests of episodic memory, verbal (phonemic) fluency, and visuomotor search and attention. Estimated premorbid intellectual functioning was assessed using the National Adult Reading Test 2nd Edition (NART-2; Nelson and Willison, 1991), which requires participants to read aloud from a list of words for which correct pronunciation differs from reading based only on phonetics. We administered the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996), which is a 15-item word list learning task, to characterise verbal anterograde encoding and retrieval, enabling us to index our sample to previous HD memory studies, which have typically employed word list learning tasks. For phonemic fluency, we asked participants to generate words beginning with a particular letter for one minute each (F, A, S; Strauss et al., 2006). The Trail Making Test (TMT; Reitan, 1958) was used to assess divided attention. The Symbol Digit Modalities Test (SDMT; Smith, 1982) was included as the most sensitive paper and pencil test for HD, enabling us to compare cognitive impairment

Table 1
Demographic information and cognitive characterisation for all participants. Mean ± Standard Deviation (Range).

	Premanifest HD	Manifest HD	Control	*p*-value	Significant group differences
Sex (F:M)	8:4	4:10	12:12	–	
Age in Years	47.25 ± 6.92 (39–56)	54.71 ± 7.61 (43–66)	50.17 ± 7.56 (39–65)	0.042*	Manifest HD > Premanifest HD
Estimated FSIQ	107.66 ± 8.04 (97–126)	108.10 ± 9.33 (95–123)	110.14 ± 9.78 (91–127)	0.69	–
CESD-R	4.83 ± 5.22 (0–16)	7.86. ± 9.40 (0–29)	8.46 ± 9.38 (0–37)	0.48	–
RAVLT Delay	9.33 ± 3.60 (2–15)	7.57 ± 2.98 (3–12)	12.17 ± 2.12 (8–15)	< 0.001*	Control > Premanifest HD, Control > Manifest HD
SDMT	50.42 ± 13.09 (34–78)	36.64 ± 10.00 (18–51)	59.42 ± 8.64 (39–72)	< 0.001*	Control > Premanifest HD > Manifest HD
Verbal Fluency	42.08 ± 11.13 (29–60)	41.86 ± 15.17 (17–63)	50.58 ± 9.95 (37–77)	< 0.001*	Control > Premanifest HD, Control > Manifest HD
TMT (B-A)^	32.10 ± 22.54 (14–88)	44.15 ± 50.59 (-5–173)	–	0.49	–

Note: * = p < 0.05. P-value based on univariate analysis of variance. Significant group differences denote significant post-hoc tests between groups. ^ TMT data only available for HD participants.
Abbreviations: HD = Huntington's disease; FSIQ = full scale intelligence quotient; RAVLT = Rey Auditory Verbal Learning Test; SDMT = Symbol Digit Modalities Test; TMT (B-A) = Trail Making Test (Part B minus Part A); CESD-R = Centre for Epidemiologic Studies Depression Scale-Revised.

severity across studies. Finally, we administered the Centre for Epidemiological Studies Depression Scale Revised (CESD-R; Eaton et al., 2004), as depression occurs frequently in HD and is associated with memory impairment (Williams et al., 2007). Select cognitive and demographic information for all participants is detailed in Table 1.

1.3. Autobiographical memory assessment

The Autobiographical Interview (AI; Levine et al., 2002) is a widely used measure of autobiographical memory performance that examines retrieval of recent and remote autobiographical events from five discrete epochs across the lifespan: early childhood (up to 11 years), teenage years (11–17 years), early adulthood (18–30 years), middle adulthood (31–55), and recent period (within the last 12-months). For each epoch, participants are required to provide a detailed description of a personally experienced event that occurred at a specific time and place, not lasting longer than 24 h in duration. For our sample, the 'middle adulthood' epoch was modified for participants under 55 years of age, whereby they were asked to retrieve an event that occurred from the age of 31 onwards, but *not within* the last 12-months to minimise overlap with the most recent period.

Consistent with the standard administration protocol, three retrieval conditions were employed, each providing increasing levels of retrieval support: *free recall*, *general probe*, and *specific probe*. During the *free recall* condition, participants spoke without interruption about their chosen memory. As needed, non-specific *general probes* were then provided to encourage more detailed recall and to clarify any instructions (e.g., "Is that everything you can remember about this event?"). After event(s) were recalled from each epoch via free recall and general probe conditions, *specific probes* targeting five discrete detail categories were provided (event, time, place, perceptual/sensory, and emotion/thought). Specific probes were provided both verbally and via written stimuli, to maximise consistency in the quality and quantity of probes provided to each participant.

1.3.1. Scoring of autobiographical memories

Interviews were digitally recorded, then transcribed, and scored. We used the standard scoring protocol for the AI (see Levine et al., 2002). Briefly, events were segmented into a series of informational details, which were then categorised as *internal* or *external*. Internal details were defined as those pertaining directly to the main event described, including information about the event that reflected a sense of episodic re-experiencing. Internal details were assigned to one of four discrete categories: event details, spatiotemporal details (time and place details combined), perceptual details, and emotion/thought details. External details were coded as: external event details (tangential information not directly related to the episode being described), semantic details, other details (i.e., metacognitive statements), and repetitions.

In keeping with the original scoring protocol, we combined free recall and general probing scores, hereafter referred to as *'free recall'*, while the total of free recall, general probe, and probed recall conditions created the *'probed recall'* composite score. AMC scored all autobiographical interviews, with 15 of these interviews randomly selected and scored by a second rater (PS) who was blind to study hypotheses and group membership, achieving the following intraclass correlation coefficients: internal free recall: 0.99, internal probed recall: 0.94, external free recall: 0.98, external probed recall: 0.94. A scored, deidentified interview sample is provided in Supplementary Materials.

1.4. Statistical analysis

Data were analysed using SPSS Version 23. Variables were assessed for normality using Kolmogorov-Smirnov tests. For our first analysis, profiles of autobiographical memory retrieval across epochs were examined using a 3 × 2 × 5 mixed design analysis of variance (ANOVA) with planned comparisons exploring group (premanifest HD, manifest HD, controls), detail type (internal, external), and epoch (early childhood, teenage years, early adulthood, middle adulthood, and the last 12-months). This analysis was run for free and probed conditions independently. We then conducted the same analyses (for both free and probed recall) using age as a covariate, because of age differences between groups.

The above analyses revealed no significant differences between premanifest and manifest HD participants on key variables of the AI. In subsequent analyses, we therefore combined the HD groups as one 'peri-manifest' HD group to increase study power and to minimise the potential confound of age on autobiographical retrieval. Non-parametric tests (Mann-Whitney's *U*) were used to examine group differences in the profile of contextual details retrieved by HD and control participants, given the non-normal distribution of the data. Finally, Pearson's correlations were run to explore associations between AI performance (specifically retrieval of internal details) and measures of HD progression (DBS, UHDRS Total Motor Score, UHDRS Total Functional Capacity, Years to Diagnosis), as well as select measures of cognitive function including delayed recall on the RAVLT, SDMT, and phonemic fluency. A conservative threshold of $p = 0.01$ was adopted to guard against Type 1 error due to multiple comparisons. Effect sizes are reported, where appropriate, using eta-squared (η_p^2).

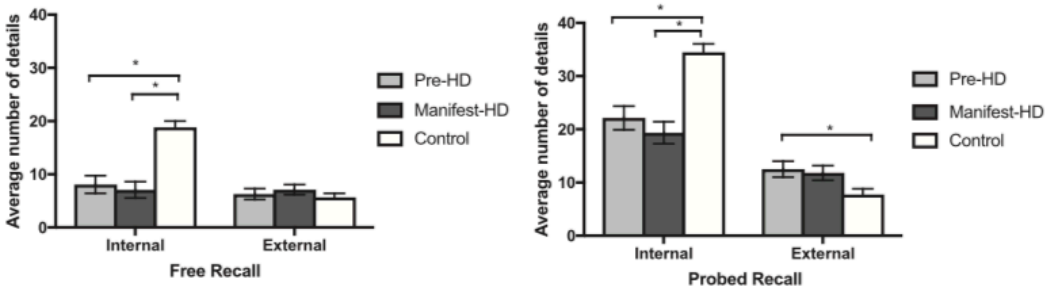

Fig. 1. Internal and external details recalled by premanifest HD, manifest HD, and control participants on the Autobiographical Interview. Details are averaged across time periods for free recall and probed recall. Error bars represent standard error of the mean. Note: Pre-HD = premanifest HD. * $p < 0.01$.

2. Results

2.1. Overall autobiographical memory performance

For the free recall condition of the AI, a group x detail type x epoch mixed-design ANOVA yielded a main effect of detail type ($F(1,47) = 52.32$, $p < 0.001$, $\eta_p^2 = 0.53$) with participants retrieving more internal than external details overall. A significant main effect of group was observed ($F(2,47) = 9.52$, $p < 0.001$, $\eta_p^2 = 0.29$), with planned comparisons revealing that controls recalled more details overall than both premanifest ($p = .001$) and manifest HD participants ($p = 0.001$), but no difference between premanifest and manifest HD groups ($p = 0.96$). A significant detail type x group interaction ($F(2,47) = 44.48$, $p < 0.001$, $\eta_p^2 = 0.65$) was also observed. As can be seen in Fig. 1, controls retrieved more internal details than both premanifest HD and manifest HD participants ($ps < 0.001$), with no difference between the HD groups ($p = 0.65$). None of the groups differed significantly from one another for recall of external details (all $ps > 0.24$). A detail type x epoch interaction approached significance ($F(4,44) = 2.42$, $p = 0.06$, $\eta_p^2 = 0.18$), however no other significant main effects or interactions including epoch were detected ($ps > 0.80$).

For the probed recall condition of the AI, a similar pattern of findings emerged, including a main effect of detail type ($F(1,47) = 189.48$, $p < 0.001$, $\eta_p^2 = 0.80$), with more internal details recalled overall ($p = 0.001$). Again, we found a main effect of group ($F(2,47) = 4.98$, $p < 0.01$, $\eta_p^2 = 0.18$) with controls retrieving more details overall than manifest HD ($p = 0.004$) and a trend towards controls retrieving more details than premanifest HD ($p = 0.05$). Again, no difference was observed in the number of details recalled by premanifest and manifest HD groups ($p = 0.43$). We also found a significant detail x group interaction ($F(2,47) = 40.20$, $p < 0.001$, $\eta_p^2 = 0.63$) with both HD groups retrieving fewer internal details compared to controls ($ps < 0.001$). Again, HD groups did not differ from one another for total internal probed recall ($p = 0.29$). Interestingly, when probed, premanifest HD provided significantly more external details compared to controls ($p = 0.02$), while a trend was detected in terms of manifest HD retrieving more external details than controls ($p = 0.08$). Again, we did not detect a difference between HD groups for external details following probing ($p = 0.48$; see Fig. 1). No other interactions or main effects were observed (all $ps > 0.42$).

We conducted the same group x detail type x epoch mixed-design ANCOVA with age as a covariate for both free and probed recall, because of the significant difference in age between groups in our sample. For free recall, we detected the same pattern of findings as reported in the absence of the age covariate, with the exception of detail type, which no longer reached statistical significance ($F(1,47) = 2.64$ $p = 0.11$, $\eta_p^2 = 0.05$). For probed recall, the pattern of findings remained the same, including all main effects and interactions reported in the absence of the age covariate.

Given the comparable profile of retrieval across the main AI metrics of interest in the late premanifest and early manifest HD groups, we combined all HD participants into one 'peri-manifest' group (n = 26) to examine profiles of contextual details (reported below). This enabled us to avoid the confound of age when comparing our findings to control participants.

2.1.1. Profiles of contextual details

Looking across the internal detail subcategories, HD participants displayed global deficits relative to controls irrespective of detail type (e.g., event, spatiotemporal, perceptual, emotion/thought), across free

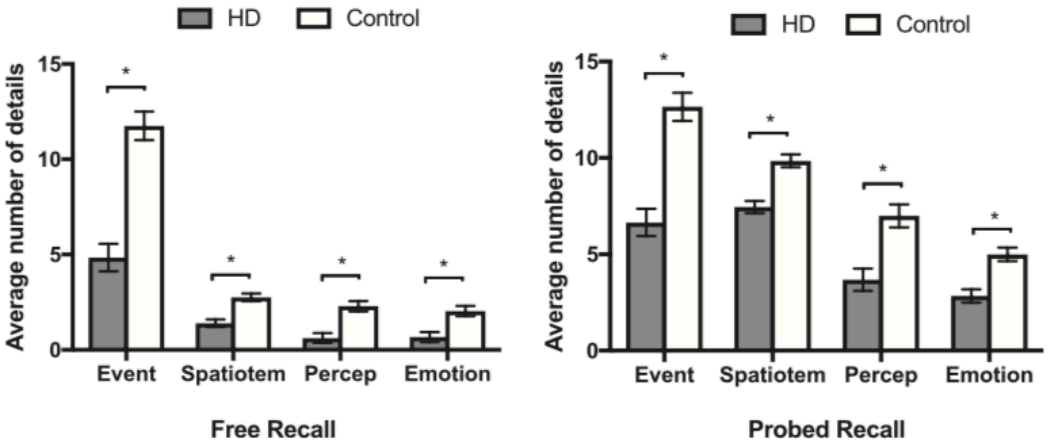

Fig. 2. Breakdown of mean internal (episodic) details retrieved by perimanifest HD and control groups across free recall and probed recall. Error bars represent standard error of the mean. Spatiotem = Spatiotemporal, Percep = Perceptual, Emotion = Emotion/Thought. *$p < 0.001$.

and probed conditions (all $ps < 0.001$; Fig. 2).

To determine whether subcategories of internal details differed within each group, we conducted a series of Wilcoxon signed-rank tests. In the free recall condition, both HD and control groups provided significantly more event details relative to all other internal detail subcategories ($ps < 0.001$). For free recall, HD participants also provided more spatiotemporal details compared to perceptual ($p < 0.001$) and emotion details ($p = 0.002$), with no further differences between perceptual and emotion details ($p = 0.66$). The control group trended towards providing more spatiotemporal details compared to emotional details ($p = 0.03$), however no other differences between subcategories were evident ($ps > 0.25$).

For probed recall, HD participants continued to provide more event details compared to perceptual and emotional details ($ps < 0.001$). People with HD further provided more spatiotemporal details compared to both perceptual and emotional details ($ps < 0.001$), and more perceptual details compared to emotional details ($p = 0.008$).

For probed recall, the control group provided more event details compared to all other subcategories ($ps < 0.001$), as well as more spatiotemporal details compared to both perceptual ($p = 0.003$) and emotional details ($p < 0.001$). Finally, more probed perceptual details were recalled by controls compared to emotion details ($p = 0.002$).

2.1.2. Profiles of external details

When comparing the subcategories of external details (e.g., external-event, repetitions, other, semantic), we found a trend towards HD participants producing more repetitions than controls ($U = 1.87$, $p = 0.06$), but no other significant group differences (all other $ps > 0.14$). Following probing, however, the HD group produced significantly more repetitions ($U = 2.87$, $p = 0.004$), and other details (e.g., metacognitive) ($U = 3.34$, $p = 0.001$) compared to controls. We also observed a trend towards the HD group producing increased semantic details relative to controls ($U = 2.53$, $p = 0.012$). See Fig. 3.

To determine whether subcategories of external details differed within each group, we again conducted a series of Wilcoxon signed-rank tests. Within the HD group, in both free and probed recall conditions, more semantic details were provided compared to all other external subcategories ($ps < 0.002$). In both recall conditions, the HD group also provided more other details compared to repetitions ($ps < 0.01$). Further, in probed recall, HD participants provided more other details compared to external event details ($p < 0.001$). No further differences were detected between other external detail categories in the HD group ($ps > 0.10$).

Controls provided more semantic details than repetitions ($p < 0.001$) or other details ($p = 0.001$) for both free and probed recall. Across both recall conditions, trends were also observed towards more semantic compared to external-event details (free recall: $p = 0.04$, probed recall: $p = 0.013$). In the free recall condition, controls provided more other details compared to repetitions ($p < 0.001$). We did not detect any other differences between external subcategories for controls across recall conditions ($ps > 0.10$). See Supplementary Materials for raw scores (means, standard deviation) for the internal and external detail subcategories.

2.1.3. Disease severity and episodic autobiographical memory

In relation to HD progression, the presence of more severe motor signs (UHDRS Total Motor Score) was associated with fewer total internal details in the probed recall condition ($r = -0.56$, $p = 0.004$). Similarly, lower functional capacity (UHDRS Total Functional Capacity) was associated with poorer probed retrieval of internal details ($r = 0.57$, $p = 0.003$). No significant association was observed between DBS and free or probed retrieval of internal details ($ps > 0.70$). Within the premanifest HD sample, estimated years to diagnosis (Langbehn et al., 2010) was not associated with total free ($r = 0.30$, $p = 0.34$) or probed ($r = 0.46$, $p = 0.14$) internal details.

2.1.4. Associations between autobiographical memory performance and other cognitive domains

We found no significant associations between cognitive measures of delayed verbal recall, executive function, or phonemic fluency and free recall of internal details (all $ps > 0.06$). For probed recall of internal details, while no significant associations survived at the conservative threshold ($p = 0.01$), we observed a trend between retrieval of probed internal details and delayed episodic recall ($r = 0.47$, $p = 0.015$) as well as phonemic fluency ($r = 0.47$, $p = 0.016$).

3. Discussion

This study is the first to demonstrate that autobiographical memory dysfunction is a pervasive feature of HD, in both its late premanifest and manifest stages. This finding is consistent with previous research in dementia syndromes (Barnabe et al., 2012; Irish et al., 2011a; Piolino et al., 2003), and provides new evidence that autobiographical memory dysfunction is present in neurodegenerative disorders characterised by early subcortical pathology. Within the HD literature, previous research has established deficits on tasks measuring anterograde episodic memory (Montoya et al., 2006; Solomon et al., 2007; Stout et al., 2011). We extend these findings to a more ecologically valid memory domain, revealing global impairments in the retrieval of personally-relevant recent and remote memories in both late premanifest and manifest HD.

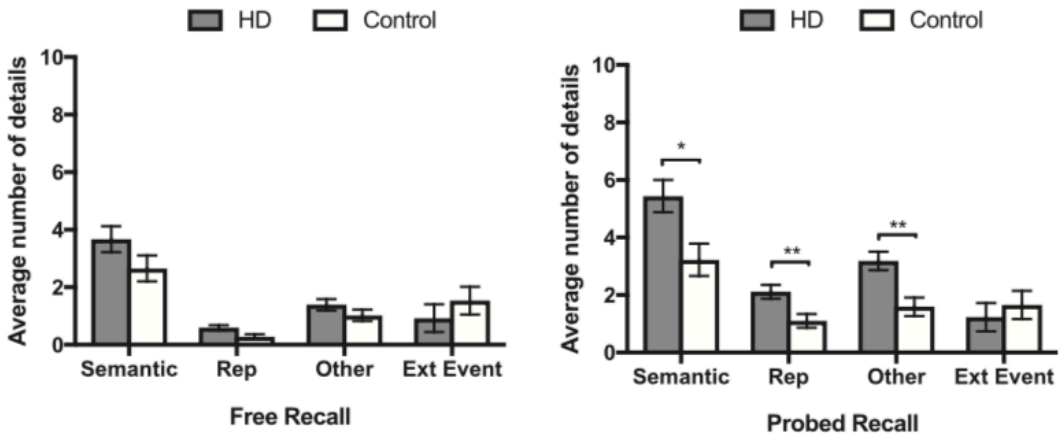

Fig. 3. Breakdown of mean external details retrieved by perimanifest HD and control groups across free recall and probed recall. Error bars represent standard error of the mean. Rep = Repetition, Ext Event = External Event. *$p < 0.05$; **$p < 0.01$.

The first key finding from our study concerns the propensity for people with HD to provide significantly fewer internal (episodic) autobiographical details relative to controls, irrespective of probing condition. Whereas specific probing (compared to free recall) yielded better recall of internal details in HD participants, even with these improvements their performance fell short of normal control levels. Interestingly, however, structured probing significantly inflated external content for premanifest HD, with a trend towards increased external details in manifest HD. Looking across both HD subgroups, these higher levels of probed (vs free) external details reflected elevated levels of repetitions and metacognitive statements, as well as a trend towards higher numbers of semantic details. Within-group comparisons revealed that semantic content dominated the external detail profile in both HD and control participants. Previous studies using the AI in dementia populations have documented compensatory increases in the provision of external details in the face of compromised retrieval of internal details (Irish et al., 2011a; Levine et al., 2002; McKinnon et al., 2008). Although some studies have demonstrated that this increase in external details reflects the production of off-target external-event details (Irish et al., 2012), in the case of HD, structured probing appears to bolster repetitions and metacognitive statements, which are not typically viewed as content-rich (Strikwerda-Brown et al., 2018). The increase in external details in HD may be a manifestation of limited cognitive control, or a general inefficiency in the focused retrieval of autobiographical information. Longitudinal studies will prove particularly important in further understanding these profiles of retrieval (e.g., Irish et al., 2018).

Turning our attention to the profile of contextual details retrieved by the HD group, global deficits were observed irrespective of internal detail type (i.e., event, spatiotemporal, perceptual, emotion/thought) or probing condition (free recall, probed recall), a finding that may reflect a general impairment in autobiographical memory specificity. Similar profiles of impairment have been reported in other neurodegenerative disorders such as frontotemporal dementia, suggested to reflect an impairment in self-referential processing (Irish et al., 2011a). We note that the impairment of emotion/thought details is of particular interest in HD, given the widespread disruption to emotional processing in this population (Kordsachia et al., 2017). As the direction of this relationship remains unclear, longitudinal studies may offer some insights into the interplay between emotion processing deficits and autobiographical memory dysfunction in the earliest stages of HD. Determining whether the valence and emotional re-experiencing of autobiographical memories are further altered in HD remains to be investigated and we suggest that studies incorporating phenomenological assessments will prove particularly informative in this regard (Irish et al., 2011b; Piolino et al., 2003). Moreover, it will be important to determine how the subjective experience of recollection is altered in HD and how this, in turn, impinges upon the individual's sense of self, given the close relationship between autobiographical memory retrieval and sense of continuity across subjective time (e.g., Prebble et al., 2013).

Interestingly, we did not find any significant epoch effects in relation to autobiographical memory performance in this study, resulting in a flat gradient across time periods in both HD and control participants. This finding is consistent with research in remote memory in HD, which has reported comparable profiles of both remote and recent memories for public events and famous faces (Albert et al., 1981; Beatty et al., 1988). Notably, however, previous studies of autobiographical memory using the AI in aging and clinical populations have reported recency effects, whereby recently experienced events are recalled in significantly greater contextual detail relative to their remote counterparts (e.g., Esopenko and Levine, 2017; Levine et al., 2002). We tentatively suggest that our modification to the 'middle adulthood' period to accommodate for varying age groups in our sample may have influenced the profile of results, however, we note that similar findings to the current study have been documented in other dementia populations (e.g., Irish et al., 2011a).

In terms of candidate mechanisms driving autobiographical memory disruption in HD, our correlational analyses did not reveal significant associations between the retrieval of internal details on the AI and neuropsychological indices of episodic memory, executive function, and phonemic fluency within the HD group. This finding is consistent with recent work that suggests that autobiographical memory performance is independent from laboratory tests of cognition (Esopenko and Levine, 2017). Moreover, our findings suggest that autobiographical memory deficits in HD cannot be explained solely by strategic retrieval or executive deficits. Replicating these findings with a more extensive battery of neuropsychological (and executive tests) will be important to further understand the specific cognitive mechanisms unpinning autobiographical memory disruption in HD.

From a clinical perspective, we did not observe significant differences in autobiographical memory function between people in the late premanifest or early manifest stages of HD, with both groups displaying marked autobiographical retrieval deficits relative to controls. This finding adds to a growing body of evidence for cognitive impairments in HD that occur prior to clinical diagnosis (Montoya et al., 2006; Robinson and Swanson, 1990; Solomon et al., 2007; Stout et al., 2011). Despite the lack of differentiation between late premanifest and manifest HD groups in terms of autobiographical memory performance, we did find an association between impaired retrieval of internal details (when probed) and more severe motor symptoms of HD. Together, this suggests the presence of autobiographical memory dysfunction in HD before motor symptoms reach the clinical threshold for diagnosis, with progressive degradation appearing as HD advances in disease severity. From a neuroanatomical perspective, we propose that autobiographical memory deficits likely reflect early atrophy in striatal regions and disruption of fronto-striatal circuitry (Vonsattel et al., 2011). This interpretation is consistent with recent findings from Esopenko and Levine (2017) who reported associations between decreased recall of internal details on the AI and reductions in bilateral middle frontal white matter regions. Given the well-established role of the MTL in supporting contextually rich ABM retrieval (Moscovitch et al., 2016), it is further possible that hippocampal dysfunction, observed in the early stages of HD (Douaud et al., 2006; Rosas et al., 2003; van den Bogaard et al., 2011), contributes to the profiles of impairment observed here. Future studies incorporating structural neuroimaging metrics will be crucial to determine the neuroanatomical substrates of autobiographical memory disruption in HD as well as furthering our understanding of the role of subcortical regions in modulating memory performance in general.

This study is the first to uncover marked deficits in the ability to retrieve personally-defining memories from the recent and remote past in HD. How such deficits impinge upon the individual's sense of self and identity remains unclear and will be an important question to address in future studies (Prebble et al., 2013). Given that autobiographical memories serve important social functions through shared reminiscing and bonding on past experiences (Alea and Bluck, 2003; Kumfor et al., 2016), we propose that future studies exploring the link between autobiographical memory disruption and interpersonal function in HD will be crucial. Finally, given the well-established links between remembering the past and the capacity to envisage the future (Schacter et al., 2013), it will be essential to understand how prospection and future-oriented thinking is potentially altered in HD, as has recently been demonstrated in other neurodegenerative disorders (Irish and Piolino, 2016). As the first study of autobiographical memory function in HD, our findings extend our understanding of the cognitive phenotype of HD.

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Declarations of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2019.02.017.

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