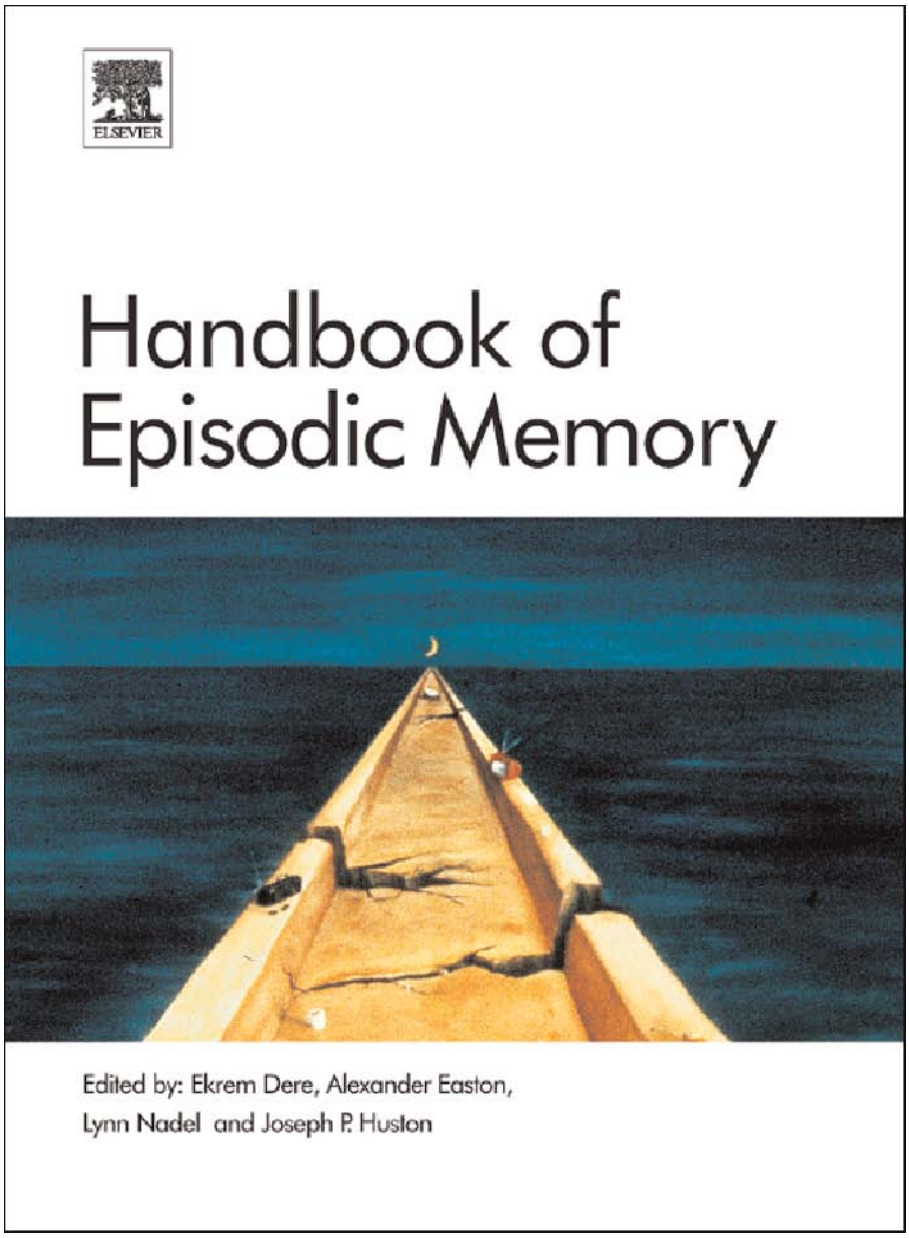

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CHAPTER 5.6

Episodic memory in the context of cognitive control dysfunction: the case of Huntington's disease

Francois Richer*, Martin Lemay and Martin Lepage

Université du Québec à Montréal, Montreal, Que., Canada

Abstract: Huntington's disease (HD) is a neurodegenerative disorder characterized by cognitive, motor, and affective symptoms. At early stages, HD is a model of progressive fronto-striatal dysfunction in which cognitive control deficits are prominent in all processing spheres including episodic memory. Early HD has little effect on episodic retention, but significantly affects intentional aspects of retrieval, and to some extent encoding and recognition. It also affects information selection and manipulation. Episodic memory impairments in HD suggest that fronto-striatal systems may have functions analogous to search engines for representations and highlight the need to better characterize the specific neural mechanisms involved in the cognitive control of memory.

Keywords: subcortical dementia; striatum; executive control; retrieval; intention; attention; chorea

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by cognitive, motor, and affective symptoms. The primary cause of the disorder is the presence of an excess of CAG repeats (over 36) in the *IT15* gene on chromosome 4 (4p16.3) which results in a polyglutamine expansion in the Huntingtin protein.

HD is characterized by cognitive, emotional, and motor symptoms which generally appear in middle adulthood with large variations in the order of appearance, evolution, and relative severity of symptoms. The clinical onset of HD is usually determined by the presence of involuntary choreiform movements often around the fourth decade. However, less apparent motor, behavioral, and cognitive changes are often present years before the emergence of chorea (Hahn-Barma et al., 1998; Snowden et al., 2002; Ho et al., 2003; Lemiere et al., 2004). The late onset of symptoms is still poorly understood but is often attributed to the breakdown of cellular adaptation mechanisms to mutant Huntingtin or to interactions with cumulative effects such as oxidative stress. Early in the disease, HD causes significant volume loss and metabolic changes in the striatum (Harris et al., 1996; Aylward et al., 1997; Bäckman et al., 1997). Other early changes include cortical thinning (Rosas et al., 2002), white matter anomalies (Rosas et al., 2006) as well as changes in neuromodulatory systems including pre- and post-synaptic changes in the dopaminergic system (Bäckman et al., 1997; Ginovart et al., 1997; Andrews et al., 1999; Pavese et al, 2003). Several studies have shown a link between the duration or severity of HD and striatal changes (Kuwert et al., 1990; Harris et al., 1996; Sax et al., 1996; Ginovart et al., 1997) as well as cortical

*Corresponding author.
E-mail: Francois.Richer@uqam.ca

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changes (Harris et al., 1996; Bäckman et al., 1997; Ginovart et al., 1997; Pavese et al., 2003).

During evolution, pathophysiological changes also occur in many regions, including the cortex, thalamus, amygdala, and mesencephalon (de la Monte et al., 1988; Kuwert et al., 1990; Mann et al., 1993; Sax et al., 1996; Bäckman et al., 1997; Ginovart et al., 1997; Rosas et al., 2002; Pavese et al., 2003; Kassubek et al., 2005). Medial temporal cortex damage is less clear than other structural changes in HD (Halliday et al., 1998), but volume reductions can be detected in MRI studies in HD patients even at early to moderate stages (Jernigan et al., 1991; Rosas et al., 2003).

Pathophysiological data suggest that early HD produces a significant disruption of cortico-striatal circuits which have an important role in frontal cortical functions because frontal cortex is the main cortical target of the striatum. This view is supported by similarities in the cognitive symptoms produced by frontal cortical lesions, acute striatal damage, and early HD. Early HD has thus long been considered a prototypical disorder of fronto-striatal systems. However, even in its early stages, HD cannot be considered as a strictly striatal or subcortical disorder and some symptoms may be linked to non cortico-striatal brain systems affected in HD or to more indirect network disruptions. Also, as is often the case in neurodegenerative diseases, symptom progression is far from uniform and different patient samples may differ in the range of severity or evolution, which may complicate comparisons across studies.

I. The cognitive profile of HD

Cognitive deficits are an early manifestation in HD. The most obvious are disturbances in cognitive control or executive functions (Lawrence et al., 1996, 1999; Roman et al., 1998; Snowden et al., 2001; Richer et al., 2002; Lemiere et al., 2004) and delayed recall of information (Butters et al., 1978, 1986, 1994; Josiassen et al., 1983; Mohr et al., 1991; Kirkwood et al., 2001). Cognitive control deficits are a heterogeneous and variably defined set of symptoms which affect several functional domains including voluntary actions (selection, planning, and execution) and attention. Because of the importance of these functions for performance in daily activities, cognitive control deficits have a significant impact on autonomy.

The cognitive profile of early HD can easily be distinguished from that of amnesic syndromes and Alzheimer's disease (AD) because of a normal rate of forgetting or retention in HD at least until late stages of the disease (Butters et al., 1983, 1985; Moss et al., 1986; Delis et al., 1991; Lundervold et al., 1994). Evidence concerning encoding problems in HD is mixed. Early observations suggested a significant problem in encoding information in HD (Butters et al., 1978; Caine et al., 1978; Weingartner et al., 1979). However, there is evidence that HD patients benefit from encoding cues (e.g., high-imagery words) significantly more than AD patients and show normal release from proactive interference (Beatty and Butters, 1986; Wilson et al., 1987; Granholm and Butters, 1988). Nevertheless, the intentional use of encoding cues can be problematic in HD (Lundervold et al., 1994). This is consistent with the significant voluntary attention problems in HD.

HD patients typically show significant difficulties recalling previously learned information, and their performance often improves significantly when their memory is tested in a recognition format especially early in the disease (Butters, 1984; Martone et al., 1984; Butters et al., 1985, 1986; Moss et al., 1986; Delis et al., 1991; Lundervold et al., 1994). Such differences between recall and recognition performance have often been attributed to the increased demands on retrieval mechanisms of recall tests relative to recognition tests (e.g., Butters et al., 1994). This retrieval impairment has been used to differentiate the memory deficits in HD from other disorders (Butters et al., 1987; Hodges et al., 1990) and particularly AD (Massman et al., 1990; Zakzanis, 1998; Salmon and Filoteo, 2007). For instance, compared to patients with Alzheimer's disease (AD), and alcoholic Korsakoff's syndrome (KS), HD patients perform substantially better on yes/no recognition of word lists, despite equivalent recall performance (Delis et al., 1991). The retrieval hypothesis is consistent with the relatively normal forgetting rate in HD. However, there is

evidence that recognition is significantly affected in HD (Beatty and Butters, 1986; Caine et al., 1986; Heindel et al., 1989; Lang et al., 2000) and that a substantial benefit of recognition over recall is not observed in a large majority of HD patients (Zizak et al., 2005).

A meta-analysis of 48 studies of episodic memory in HD found a significant difference between HD patients and controls on recognition memory performance even in patients with milder cognitive symptoms (Montoya et al., 2005). Patients with milder cognitive symptoms did show a greater deficit in recall than in recognition but not patients with moderate or advanced dementia. Thus, compared to AD and KS, the benefit of the recognition format is present in early HD, but recognition problems are part of HD and should be taken into account in models of episodic memory in HD. As observed in HD, frontal cortex damage also produces recognition difficulties and a gradient of difficulty between free recall, cued recall, and recognition (Wheeler et al., 1995). The presence of significant recognition errors is not necessarily inconsistent with a retrieval deficit in HD. In fact, an increased rate of false positive recognition errors has been observed in certain tasks, suggesting an impairment in effortful retrieval (Bylsma et al., 1991). Also, explicit recognition judgments show several similarities to choice responses that can produce cognitive control errors in HD patients.

Retrieval demands may not be the only factor contributing to the memory deficits in HD. Some processes contributing to recognition, such as recollection ability, could be affected early in the disease while other processes such as familiarity judgments may be relatively preserved until general cognitive impairment has progressed. This hypothesis will have to be experimentally confirmed. One study showed that HD patients could accurately predict whether or not they would be able to recognize unrecallable information, suggesting a relatively preserved ''feeling-of-knowing'' at least in some contexts, but they appeared unable to use this knowledge to increase their recall performance as controls did (Brandt, 1985). To the extent that the feeling of knowing contributes to familiarity judgments, this observation provides preliminary support for the relative preservation of familiarity-based recognition in HD. However, there are little data on recollection ability and the associated processes of autonoetic consciousness (the re-experience of the acquisition context) in HD and these would be needed to better characterize recall and recognition deficits in this population.

Remote memory is clearly affected in HD after early stages. When present, retrograde amnesia in HD is clearly distinct from that observed in AD in that it does not appear to show a temporal gradient across decades and benefits more from cuing (Beatty et al., 1988; Sadek et al., 2004). These data are also consistent with a spared consolidation and an impaired retrieval in HD. The retrieval hypothesis is also consistent with the documented deficit in verbal and nonverbal fluency in HD, characterized by a poor recall of semantic or relational information (e.g., Snowden et al., 2001).

Some have suggested that episodic memory in HD patients is disturbed in relation to the mental effort involved in the task (Wilson et al., 1987; Lundervold et al., 1994). A related suggestion is that memory performance in HD is linked to a deficit in the cognitive control of memory processing (Moscovitch, 1992; Richer and Chouinard, 2003). The retrieval deficit in HD shows many parallels with the cognitive control deficits which are a hallmark of HD. Cognitive control deficits affect many functions including perception and action through an impaired regulation of processing by top–down representations such as behavioral goals and perceptual templates. These top–down representations provide bias signals which modulate processing including the selective activation of representations among competing alternatives. For example, in perception, there is evidence that fronto-striatal circuits interact with sensory cortical regions to bias their activity according to goals and response rules (Fuster, 1997; Miller and Cohen, 2001). This biasing activity helps select target objects among competing stimuli. In fronto-striatal disorders, these processes are often disrupted, slowed, or sensitive to interference. Cognitive control symptoms are most apparent when fronto-striatal signals are

critical as in (1) unfamiliar contexts containing weak or ambiguous cues, (2) when there is interference from competing stimuli or responses, or (3) when the time demands or processing demands are high. Even when an activity is well practiced, cognitive control processes may still be needed during brief intervals at critical decision points.

Cognitive control deficits have well-documented effects on intentional action selection and on attention-based perceptual selection. However, both action selection and perceptual selection fundamentally involve retrieval of the most relevant representations for a specific task. Episodic retrieval deficits in HD also share many common features with cognitive control deficits observed in HD including an association with top–down control variables such as retrieval cues and goals and a sensitivity to interference. Although they are less well understood, cognitive control mechanisms recruited by retrieval cues could help selectively retrieve the appropriate response in episodic recall. As discussed before, HD patients can show difficulties using retrieval cues or strategies that favor recollection (Brandt, 1985). Also, HD patients show more problems with the intentional use of encoding cues than with automatic encoding. HD patients also show problems recalling the source and context of information encoding like those described in patients with frontal cortex lesions (Brandt et al., 1995). Many of these problems are consistent with an inefficient cognitive control of remembering. Bringing relevant information to mind and resolving competition between retrieved representations on the basis of relevance are critical steps in selecting goal-directed behavior. These functions are analogous to those of search engines in digital databases with search efficiency being dependent on the sensitivity and sophistication of control cues, interference filters, and search algorithms. There is growing evidence that prefrontal systems are involved in these memory control functions (e.g., Badre et al., 2005). HD may impair critical retrieval control processes which are dependent on prefrontal cortex activity or on fronto-temporal interactions. Future studies should investigate retrieval, recognition, and encoding problems in HD as outcomes of specific fronto-striatal mechanisms involved in the cognitive control of memory.

II. HD and multiple learning systems

In addition to problems involving cognitive control and information recall, HD has also long been associated with the dissociation of explicit learning (episodic, semantic, contextual, or relational) and more implicit sensorimotor (procedural) learning. There are indications that HD affects performance in some tasks that require acquisition of sensorimotor skills such as predictable visuomotor tracking (Gabrieli et al., 1997) but this is far from generalized and normal acquisition has been reported in several tasks (Willingham and Koroshetz, 1993; Smith and Shadmehr, 2005). For other tasks, such as implicit sequential response learning, the evidence is unclear (Knopman and Nissen, 1991; Willingham and Koroshetz, 1993; Brown et al., 2001) and there is evidence that intentional aspects of sequential response learning and performance are affected (Brown et al., 2001). Sensorimotor or procedural acquisition problems are often difficult to dissociate from intentional performance or cognitive control problems and the latter may contribute to many measures aimed at indexing sensorimotor acquisition. Thus, while the issue of implicit learning problems in HD is not yet resolved, these problems are not a hallmark symptom of early stage HD in the same sense that cognitive control problems and explicit recall are hallmark problems in HD.

III. Preclinical memory deficit: when do problems start?

Loss of striatal volume has been reported in preclinical carriers of the HD gene up to 11 years before the estimated onset of the disease (Aylward et al., 1994, 2004). Up to 5% shrinkage per year has been observed in patients with HD and striatal atrophy is a good predictor of individuals who will present clear symptoms within 2 years (Aylward et al., 2004). We still know little of the progression of the deficits before clinical onset and evolution is variable, but cognitive deficits are

often detectable a few years before clear motor symptoms are present.

Diverse cognitive changes have been observed in presymptomatic HD gene carriers, affecting functions such as attention and cognitive control (Campodonico et al., 1998; Lemiere et al., 2004). While some studies have reported the presence of memory deficits in presymptomatic HD gene carriers (Lundervold and Reinvang, 1995; Rosenberg et al., 1995; Campodonico et al., 1998; Diamond et al., 1992; Hahn-Barma et al., 1998; Berrios et al., 2002; Lemiere et al., 2004), others have found only subtle differences (Snowden et al., 2002) or no differences (Strauss and Brandt, 1990; Rothlind et al., 1993; Lawrence et al., 1998; de Boo et al., 1999). The discrepancies could be related to variations in the pre-clinical progression of the disease (time to clinical onset) or to a small effect size. A recent study on a large sample of 490 asymptomatic gene-carriers showed lower verbal recall (HVLT-R) scores in preclinical gene-carriers as compared to healthy controls, especially in patients less than 5 years from the estimated clinical onset (Solomon et al., 2007). Both episodic encoding and retrieval were reported to be affected but not storage. Also, lower HVLT-R scores were associated with smaller striatal volume in that study. Striatal as well as cortical atrophy have shown significant correlations with poorer performance in a memory task (Starkstein et al., 1992) as well as in a speeded mental processing task (Campodonico et al., 1998).

Overall, it appears that retrieval and encoding problems can be observed in HD-gene carriers a few years before clear clinical signs and that these deficits are related to neurodegeneration in both striatum and cortex.

IV. Episodic memory and behavior in HD

Psychiatric symptoms including apathy, behavioral dysinhibition, depression, anxiety, and irritability are present at least intermittently in many patients with HD as well as in presymptomatic gene-carriers (Cummings, 1995; Paulsen et al., 2001; Marshall et al., 2007). Behavioral symptoms are relatively independent from cognitive or motor symptoms and appear to evolve differently during the progression of the disease (Zappacosta et al., 1996; Paulsen et al., 2001). Whereas behavioral symptoms cannot be considered as the main factor explaining cognitive deficits in HD, they could contribute to their expression. Depressive and anxiety symptoms are prevalent in HD and could contribute to episodic memory symptoms (Lemogne et al., 2006; Payne et al., 2006). Also, apathy is present in more than 50% of patients with HD and can affect many cognitive functions including episodic memory. One study showed that verbal recall and recognition performance is more impaired in apathetic patients with HD as compared to patients that were not apathetic independently of depressive symptoms (Baudic et al., 2006).

In summary, early HD has provided a good model for a fronto-striatal profile of episodic memory deficits with relatively preserved consolidation and poor retrieval. Encoding problems are more difficult to characterize, but they also appear to mainly affect intentional information selection at first and to spare the automatic use of encoding cues. Recognition problems, while present, need to be better characterized especially in their links to more specific processing such as recollection and to fronto-striatal functions in general. HD has helped shape our conception of the architecture and neuroanatomy of explicit memory. Memory in HD is somewhat analogous to a poor search engine applied to databases that can still be updated relatively well. We now need to move beyond neuropsychological description and into the specific fronto-striatal mechanisms preventing correct retrieval, recognition, and encoding in HD.

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