

# Episodic memory impairment in Huntington's disease: A meta-analysis

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## Abstract

Memory dysfunction is an important feature in the clinical presentation of Huntington's disease (HD) and may precede the onset of motor symptoms. Although several studies have contributed to the quantitative and qualitative description of memory impairments in HD, the characterization of episodic memory impairments has varied considerably. Whereas most studies report significant impairments on free recall tests, performance on recognition tests has been considerably more variable, ranging from normal to markedly deficient. This absence of a well-established recognition memory deficit has led some investigators to attribute the memory deficits in HD to a retrieval-based episodic memory impairment. We felt that a quantitative review of the literature was needed to better characterize these episodic memory impairments. We conducted a meta-analysis to assess the magnitude of the recognition memory deficit in HD and to examine it in relation to the known deficit in recall. Memory data were provided by 544 symptomatic HD patients, 224 presymptomatic gene-carriers, and 963 control subjects. The overall group comparison between symptomatic patients and controls yielded effect sizes of  $d = 1.95$  for free recall and  $d = 1.73$  for recognition. We split the symptomatic group into two subgroups based on their mental status (mild and moderate/severe dementia) and both showed significant deficits in recall and recognition memory, though recall was more impaired than recognition in the mild dementia subgroup. Only slight memory impairment was observed in the presymptomatic subjects. The results show that deficits in recognition memory must be accounted for in future models of memory impairment in HD.

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## 1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder clinically characterized by progressive involuntary movements, neuropsychiatric disturbances and cognitive impairment. At a molecular level, the disease is caused by the abnormal expansion of a CAG trinucleotide repeat within the IT15 gene located on chromosome 4 (Group, 1993). HD is characterized neuropathologically by widespread neuronal degeneration occurring earliest in the striatum then spreading elsewhere, with significant involvement of the cortex and other extrastriatal regions and important disruption of the fronto-subcortical circuitry (Aylward et al., 1996, 1998; de la Monte, Vonsattel, & Richardson, 1988; Harris et al., 1992; Rosas et al., 2002, 2003;

Selemon, Rajkowska, & Goldman-Rakic, 2004; Vonsattel et al., 1985).

From a neuropsychological perspective, the disease affects several cognitive domains and results in disturbances in attention (Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Butters, Wolfe, Granholm, & Martone, 1986), executive functioning (Brandt, Bylsma, Aylward, Rothlind, & Gow, 1995), and memory (Brouwers, Cox, Martin, Chase, & Fedio, 1984; Butters, Salmon, & Heindel, 1994; Kirkwood, Su, Conneally, & Foroud, 2001; Mohr et al., 1991; Oscar-Berman, Zola-Morgan, Oberg, & Bonner, 1982). Much of the interest in examining memory impairment in HD derives from the findings that such deficits are prominent in the earliest stages of the disease process (Butters, Sax, Montgomery, & Tarlow, 1978; Josiassen, Curry, & Mancall, 1983) and that they can have a significant impact on the lives of the individuals touched by the disease, affecting their ability to work, manage a household or properly care for themselves (Caine, Hunt, Weingartner, & Ebert, 1978).

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It is now accepted that memory comprises several distinct and interacting systems (Cohen & Squire, 1980; Graf & Schacter, 1985; Tulving, 1983). One such system, episodic memory, is known to be remarkably disturbed in dementia (Beatty et al., 1988; Butters, Granholm, Salmon, Grant, & Wolfe, 1987). Episodic memory includes memories for personal experiences and events that are dependent upon temporal and/or spatial cues for their retrieval (Tulving, 1983). Episodic memories are typically measured by direct or explicit tests that refer to a prior episode, such as free recall, cued recall, or recognition tests (Graf & Schacter, 1985; Yonelinas, 2001). Some of the most common tests used to measure episodic memory in HD are tests of verbal learning and memory, including the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987) and the Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1995), as well as tests of immediate and delayed verbal and nonverbal memory, such as the Logical Memory, Visual Reproduction, and Paired Associates subtests of the Wechsler Memory Scale (WMS) (Wechsler, 1987, 1997). It is generally held that deficits in episodic memory may arise from deficiencies in the encoding of information, susceptibility to interference of competing information, failure to consolidate information for long-term storage, and/or the inefficient retrieval of successfully stored information.

A great number of studies have contributed to the quantitative and qualitative description of episodic memory in HD and this work has led to tremendous insights into the memory abilities of affected individuals. Early observations directed interest towards the patients' inability to recall information (Butters & Grady, 1977; Butters et al., 1978; Caine et al., 1978) and led to the hypothesis of a retrieval deficit related to impairments in storage (Butters & Grady, 1977) and encoding (Weingartner, Caine, & Ebert, 1979). In the years that followed, a number of studies were carried out that reinforced this concept of a retrieval-based memory deficit in HD and concurrently attempted to uncover its roots. Several studies found evidence supporting intact storage or retention in HD, while at the same time continuing to find performance on recall tasks to be severely impaired (Butters et al., 1983; Butters, Wolfe, Martone, Granholm, & Cermak, 1985; Delis, Massman, Salmon, Cermak, & Kramer, 1991; Lundervold, Reinvang, & Lundervold, 1994; Moss, Albert, Butters, & Payne, 1986). In one such study, Butters and colleagues (Butters et al., 1985) assessed verbal recall memory in HD patients relative to alcoholic Korsakoff's syndrome (KS) patients and healthy control subjects. Although the HD group displayed an equivalent level of impairment to the KS group on a modified recall form of the RAVLT, they demonstrated an increased ability to learn during the five presentation-recall trials and a lower rate of forgetting over a 20 min delay than the KS patients. At roughly the same time, Beatty and Butters (1986) re-examined the encoding hypothesis in HD by both manipulating the imageability of words to be recalled and recognized, and assessing patients' susceptibility to interference from competing information (using distractor paradigms to assess release from proactive interference). Although patients recalled significantly fewer words than controls in both tasks, their performance was improved for words that received high imagery ratings and they

exhibited a normal release from proactive interference, suggesting that their ability to encode verbal and semantic information was still intact (Beatty & Butters, 1986). However, possibly the greatest support for a retrieval deficit in HD comes from observations and studies of these patients' performance on tests of recall and recognition memory. Several investigators, using a variety of testing paradigms, have shown that, while patients had significant difficulties recalling previously learned information, their performance improved and in some cases reached normal levels when their memory was tested in a recognition format (Butters, 1984; Butters, Wolfe, Granholm, & Martone, 1986; Butters et al., 1985; Caine et al., 1978; Delis et al., 1991; Lundervold et al., 1994; Martone, Butters, Payne, Becker, & Sax, 1984; Moss et al., 1986). This notion of a retrieval-based episodic memory impairment has been used by some investigators to differentiate the neuropsychological deficits in HD from those in other disorders (Butters et al., 1987) and to support the concept of 'subcortical dementia' (Massman, Delis, Butters, Levin, & Salmon, 1990; Zakzanis, 1998). For instance, when the memory profiles of patients with HD, KS, and Alzheimer's disease (AD) were examined using the CVLT (Delis et al., 1991), several important distinctions emerged. While the HD group displayed a level of immediate recall equivalent to that of the other groups, they performed substantially better than the AD and KS patients on a yes/no recognition test. Based on findings such as these, it was hypothesized (Butters, 1984; Butters et al., 1994) that the memory deficits in HD result largely from the patients' inability to initiate and carry out the systematic retrieval of successfully stored information. Such differences in recall and recognition memory performance were attributed to the significantly increased demands on retrieval mechanisms associated with recall tests relative to recognition tests.

Although there seems to be a clear impairment in recall memory in individuals with HD, the facts surrounding recognition memory are not as robust as some would suggest. Yet, despite incongruous accounts, the simplicity of this retrieval hypothesis has brought about its acceptance. For example, Zakzanis (1998) performed a meta-analysis of 36 published studies in an effort to estimate the consistency, strength, and selectivity of neuropsychological deficits in HD. He found that patients performed most poorly on tests of delayed recall (more specifically, verbal and visual delayed recall), followed by tests of memory acquisition, cognitive flexibility and abstraction, manual dexterity, attention and concentration, performance skill, and verbal skill. After contrasting the magnitude of the effect for delayed recall with an effect size for CVLT discriminability, he concluded that the pattern of results was indicative of a retrieval deficit. This particular conclusion should be interpreted with caution, as Zakzanis' aim to evaluate general neurocognitive dysfunction in HD and not any one cognitive domain in particular likely precluded a more exhaustive examination of the literature surrounding memory and HD. Consequently, his conclusions on memory are based on relatively little data, with the findings for delayed recall consisting of four effect sizes derived from only two studies and the effect size for discriminability originating from only one study.

Indeed, a number of studies have shown that patients with HD do not suffer solely from retrieval deficits and that recognition

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