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Cognitive assessment strategies in Huntington's disease research

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HIGHLIGHTS

- Cognitive assessment in HD research is an exciting and evolving field.
- After four decades of cognitive research in HD, important lessons have been learnt.
- We review the important historical developments in the study of cognition in HD.
- Important considerations when including cognitive assessment in HD research are discussed.
- Finally, we outline future directions for cognitive research in HD.

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ABSTRACT

The number of studies examining cognition in Huntington's disease (HD) has increased dramatically in recent decades, and cognitive research methods in HD have become much more sophisticated. In this review, we provide a summary of the advances in cognitive research in HD to date, and outline the key considerations for researchers planning to include cognitive assessment in their studies of HD. In particular, we discuss consideration of structure–function relationships, selection of tests appropriate to the population, choice of materials and issues of intellectual property, consideration of variables which can confound studies of cognition in HD, practice effects, and specific issues for multi-site research. Finally, we discuss future directions for cognitive assessment in HD research.

Contents

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1. Introduction

Huntington's disease (HD) is a rare, autosomal dominant, progressive neurodegenerative disease that causes motor and cognitive dysfunction, and psychiatric disturbance (Walker, 2007). Cognitive decline invariably occurs in the disease course, starting with subtle signs more than 10 years before diagnosis, progressing throughout the disease (Papoutsi et al., 2014), and affecting a broad range of cognitive domains. Whether deterioration is gradual and proceeds at a consistent rate across the disease course, or instead declines at varying rates in different disease stages is unknown. Sensitive detection and characterisation of cognitive decline in the clinical setting assists patients and their families by highlighting aspects of dysfunction for which compensatory strategies can be put into place. In the research setting, sensitive measurement of the course and nature of cognitive changes in HD illuminates the link between neuropathological progression and declines in everyday function, and provides an essential window into the effectiveness of interventions aimed at ameliorating the cognitive symptoms of HD.

Cognitive impairment in HD has been extensively studied. The first publication focussed on cognition in HD was published in 1974 (Boll et al., 1974), describing an array of changes in cognitive performance in manifest HD compared to healthy age- and gender-matched comparison subjects. Several hundred papers have now been published and more than 200 different cognitive tests have been reported in HD or at risk samples. Thus, a tremendous amount is now known about the types of cognitive impairments that occur in HD. Nevertheless, the picture of cognition in HD continues to evolve due to the complexities inherent in the myriad of cognitive processes that underlie adaptive functions in humans, ongoing theoretical developments in cognitive neuroscience, and the bewildering variety of methodological approaches that can be used to measure and characterise cognition in HD.

The aim of this paper is to capture, for the non-expert in cognitive assessment, the extent and scope of research that has been conducted on cognition in HD, including a high level overview of the methodological approaches. We begin by providing some historical context of research on cognition in HD, and how this HD research fits within the evolution of cognitive assessment methods from both clinical neuropsychology and cognitive neuroscience. We next discuss the key considerations when designing research which includes cognitive assessment in HD. This includes general considerations for all cognitive research, and then issues which are pertinent to particular research designs: cross-sectional designs, longitudinal designs, and those studies with multiple data collection sites. We finish this review with a preview of the progress we can anticipate in understanding cognition in HD by applying new methods in the coming years.

2. Historical context

Research focussing on cognition now spans four decades, with the first publication on cognitive function in HD in 1974, nearly 100 years after George Huntington's eponymous 1872 paper describing the disease, and nearly 20 years before the 1993 discovery of the gene for HD. An Ovid Medline search of terms "Huntington Disease" AND "cognition" (June 16, 2015) revealed the accelerating rate of relevant publications, with four in the 1970s, about 20 in the 1980s, about 70 in the 1990s, about 210 in the 2000s and already more than 200 additional papers in the five years since 2010. More than 200 different cognitive tests are referenced across these publications. Thus, the nature and variety of cognitive declines associated with HD are well known.

The first achievement of this literature was to demonstrate that HD is indeed associated with impairments in cognition. The first publication in 1974 studied 11 patients diagnosed with Huntington's disease using the Halstead Neuropsychological Battery, the Wechsler-Bellevue Scale, and the Trailmaking Tests (Boll et al., 1974). Even with only a small sample, the authors demonstrated clear and wide-ranging effects not only on tasks requiring motor performance, "but also on the areas of memory, problem solving, concept formation, verbal storage, alertness, and concentration." (p. 68). Five years later, in 1979, Nancy Wexler published the first investigation of cognitive function in people at genetic risk for HD (Wexler, 1979).

Beyond establishing objective evidence of cognitive dysfunction in HD, a key paper in 1977 (Caine et al., 1977) provided an initial outline of memory impairment in HD, which documented for the first time the inefficiency in learning and retrieval of information from memory. In this paper they articulate the view, still held today, that memory deficits in HD are characterised by significant difficulty with encoding new information. This, in turn, affects retrieval, seen most prominently in free recall trials. Semantic cueing or a recognition format tends to aid retrieval. This pattern of memory deficits is mild in the beginning stages of the disease, but worsens and becomes more inclusive as the disease progresses.

In the subsequent decade, the 1980s, about 20 papers relevant to cognition were published, addressing memory profiles, as well as how cognitive impairments in HD compared to other neurodegenerative diseases. The distinction between cortical dementias, mainly Alzheimer's disease, and subcortical dementias, namely Parkinson's disease, was popularised during that period, and several papers on HD appeared that argued that the memory and other aspects of the cognitive profile in HD were more similar to subcortical than to cortical disorders, with storage of memories relatively preserved, but inefficient retrieval from memory. Studies during this period continued to feature small samples (i.e., usually fewer than 20 subjects), and were aimed at characterising the basic nature of cognitive impairment associated with HD.

Published HD research in the mid-1980s through to the 1990s continued to develop the picture of cognition in HD. During this time, a debate was waged regarding the existence of cognitive decline prior to HD diagnosis. Because the gene for HD had not yet been identified, this debate was fuelled by the reliance on subject samples that were inevitably heterogeneous due to the need to include subjects who were at risk only on the basis of having a parent with clinically or pathologically confirmed evidence of HD. Around 50% of individuals included this way could be presumed not to have the gene for HD. The debate was further fuelled because the reality of small sample sizes in these early local studies, due to the rare nature of the disease, meant that only large effects of cognition in the premanifest gene carriers were detected, along with a tendency toward false negative results. Large effect sizes for differences between at risk groups and controls would not be expected, given that evidence thus far suggested the people with HD start from a normal baseline and only gradually do signs and symptoms appear.

The discovery of the gene for HD in 1993 and subsequent availability of a PCR-based test for HD brought the opportunity for clarity regarding the presence of cognitive decline prior to HD diagnosis. Serendipitously, Foroud and colleagues had assembled a large cohort for a genetic linkage study, which included assessment on the Wechsler Adult Intelligence Scale-Revised (WAIS-R). Once the gene test became available, they quantified the HD-CAG repeat expansion numbers, allowing for the first time, an examination of cognitive function in a large, relatively pure sample of individuals at genetic risk for HD (Foroud et al., 1995). The study yielded two key findings: (1) on two WAIS-R subtests (Digit Symbol and Picture Arrangement), CAG-expansion in the absence of manifest