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Research report

Cortical inhibitory deficits in premanifest and early Huntington's disease

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HIGHLIGHTS

- Understanding pathophysiology in HD may provide new insights on disease mechanisms.
- We studied the largest premanifest and symptomatic HD sample with TMS to date.
- Cortical inhibitory deficits were observed in both premanifest and symptomatic HD.
- Reduced GABAergic inhibition in HD was correlated with the triad of symptomology.
- TMS is a useful tool for investigating pathophysiology in HD.

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ABSTRACT

Although progress has been made towards understanding the gross cortical and subcortical pathology of Huntington's disease (HD), there remains little understanding of the progressive pathophysiological changes that occur in the brain circuits underlying the disease. Transcranial magnetic stimulation (TMS) enables investigation of the functional integrity of cortico-subcortical pathways, yet it has not been widely applied in HD research to date. This study sought to characterise profiles of cortical excitability, including inhibition and facilitation, in groups of premanifest and symptomatic HD participants via the use of TMS. We also investigated the clinical, neurocognitive and psychiatric correlates of cortical excitability to better understand the development of phenotypic heterogeneity. The sample comprised 16 premanifest HD, 12 early symptomatic HD and 17 healthy control participants. Single- and paired-pulse TMS protocols were administered to the left primary motor cortex, with surface electromyography recorded from the abductor pollicis brevis muscle. Short-interval cortical inhibition was significantly reduced in symptomatic HD, compared with premanifest HD and controls, and was significantly correlated with pathological burden and neurocognitive performance. There was also reduced long-interval cortical inhibition in both premanifest and symptomatic HD, compared with controls, which was associated with pathological burden and psychiatric disturbances. Motor thresholds, cortical silent periods and intracortical facilitation did not differ across groups. Our results provide important new insights into pathophysiological changes in cortico-subcortical circuits across disease stages in HD. We propose that neurophysiological measures obtained via TMS have potential utility as endophenotypic biomarkers in HD, given their association with both pathological burden and clinical phenotype.

1. Introduction

1.1. Huntington's disease

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an expansion of CAG repeats in the huntingtin gene. The pathogenic process primarily involves the basal ganglia

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and cerebral cortex [1]. In particular, there is early dysfunction and loss of GABAergic striatal neurons, causing a constellation of motor, cognitive and psychiatric signs. Clinical diagnosis of HD (symp-HD) by observation of involuntary choreiform movements typically occurs in middle adulthood. Gene-positive premanifest HD (pre-HD) individuals exhibit a range of neuropathological changes 15–20 years prior to clinical onset [2], whereas neurocognitive, psychiatric and subtle motor signs are evident <10 years prior [3]. Despite the wealth of knowledge about the gross pathology of HD at different disease stages, there remains little information regarding the pathophysiological properties of neurons within cortico-subcortical circuits underlying the disease. Such information may provide critical new insights on how neurons progress to death in HD.

1.2. Transcranial magnetic stimulation

GABA is a common inhibitory neurotransmitter with widespread functions mediated by $GABA_A$ and $GABA_B$ receptors in cortical and subcortical regions [4]. Transcranial magnetic stimulation (TMS) is able to assess the functional integrity of cortico-subcortical circuits noninvasively, by generating a magnetic field that penetrates the skull and depolarises neurons. Following motor cortex stimulation, amplitudes of motor-evoked potentials (MEPs) from TMS can be recorded through electromyography (EMG) in a peripheral muscle, and manipulated via changes in stimulus intensity and other parameters [5]. The hyperpolarisation of postsynaptic neurons via $GABA_A$ receptors can be assessed with the well-established short-interval cortical inhibition (SICI) paradigm, whereas both long-interval cortical inhibition (LICI) and cortical silent period (CSP) protocols probe $GABA_B$ receptor-mediated circuits [6]. It is widely recognised that TMS is useful for understanding pathophysiology in a range of neurological disorders and in establishing functional biomarkers, yet its application in HD to date has been limited [7].

1.3. Pathophysiology in HD

Previous structural and functional magnetic resonance imaging (MRI) studies have shown cortical thinning in HD, as well as regionally-selective cortical changes, especially in motor cortices [8]. TMS enables investigation of both the pathophysiological results of cortical thinning and the functional impact of regional cortical changes. TMS–EMG has been applied in HD using a number of approaches, including exploring cortical excitability with single- and paired-pulse protocols [9–14]. However, none of the previous studies included a comprehensive protocol of TMS measures in order to establish and compare the profile of corticospinal excitability, including cortical inhibition and intracortical facilitation (ICF), in pre-HD and symp-HD participants. For example, investigating both SICI and LICI, in the resting muscle, might enable the isolation of specific GABAergic deficits without pre-existing synaptic activity. This is an important feature if we are to further delineate the pathogenic mechanisms in terms of axonal and synaptic effects, and extend our knowledge of cortico-subcortical changes.

It has been argued that HD is associated with a disturbed balance of inhibitory and facilitatory connections, which may manifest phenotypically in the heterogeneous expression of symptoms [15]. This disturbed balance may impair the brain's capacity to produce an integrated response following TMS, thereby leading to reduced responses across multiple neural pathways and/or phenotypic measures. However, while animal models support early disturbances in cortical interneuronal activity [16], there is no conclusive evidence from human participants to support this conjecture. Mixed TMS findings for humans are likely to have resulted from a multitude of factors, including differences in sample constitution, coil types, current direction, stimulus intensities and muscle activation. Moreover, comparison between studies is problematic because the various TMS measures employed tap into different mechanisms, which makes interpretation of the literature complex. This is particularly true when studies make inferences based on a select few measures, which may not reflect the full range of pathophysiological deficits in HD. The two TMS studies that directly compared pre-HD and symp-HD participants did not elicit group differences and postulated that neurophysiological abnormalities were caused by the presence of the gene mutation in the brain during development, as opposed to degenerative effects [14,17]. In contrast, numerous studies have demonstrated neurophysiological decline in HD across a range of non-TMS measures, including evoked synaptic responses, which also correlate with increasing clinical severity with disease progression [18,19]. Thus, the question of what pathophysiological abnormalities typically develop in HD, and whether these occur in parallel with the development of types of symptomology, remain unanswered. More comprehensive investigation of pathophysiology in pre-HD and symp-HD participants, that encompass a broad range of disease stages, together with increased neurocognitive and psychiatric phenotypic characterisation, is therefore warranted.

1.4. Aims and hypotheses

The aim of the present study was to examine and compare pathophysiological changes in pre-HD and symp-HD. Seven relevant TMS measures were investigated; specifically, the resting and active motor thresholds (RMT and AMT, respectively), the CSP (at two stimulus intensities), SICI, ICF and LICI. Our aim was achieved, firstly, by characterising a profile of excitability, inhibition and facilitation in samples of pre-HD and symp-HD participants, and secondly, by investigating the clinical, neurocognitive and psychiatric correlates of TMS measures. To our knowledge, this is the first study to utilise a comprehensive TMS procedure in pre-HD as well as symp-HD groups, and to investigate relationships between TMS measures and the triad of symptoms that characterise HD (as indexed by a number of neurocognitive and psychiatric instruments). In particular, we seek to replicate past TMS findings in symp-HD and to build upon the seminal work of Schippling et al. [14], which investigated the RMT and AMT, the CSP and SICI in 16 pre-HD and symp-HD participants. We build upon this work by including ICF, LICI and a range of neurocognitive/psychiatric measures. Moreover, we also used a grip force transducer, investigated a target muscle with lower inter-trial variability [20] and recruited a gender-balanced sample to refine the methodology of the Schippling et al. study. It was hypothesised that corticospinal excitability, cortical inhibition and ICF would be reduced in symp-HD compared with pre-HD, which in turn would be reduced relative to healthy controls. It was also hypothesised that reductions of TMS measures would be associated with greater clinical severity, poorer neurocognitive performance and increased psychiatric symptoms.

2. Material and methods

2.1. Participants

The sample comprised 45 participants, consisting of 16 pre-HD (age range = 26–54 years), 12 symp-HD (43–69 years) and 17 healthy controls (26–57 years). Controls were matched for age and gender to the pre-HD group. One-way ANOVA revealed that the symp-HD group was significantly older than both the pre-HD and control groups. There were no significant differences in gender across groups. Moreover, there were no significant differences in IQ scores (National Adult Reading Test—2nd edition) [21], years of