Evaluation of Cognition and Cortical Excitability in Huntington’s Disease

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ABSTRACT: Background: Recent advances in neurophysiological techniques have contributed to our understanding of the pathophysiology of Huntington’s disease (HD). Studies of the motor cortical excitability and central motor pathways have shown variable results. Objectives: Our aims were to evaluate the cortical excitability changes in HD using transcranial magnetic stimulation (TMS) and correlate the changes with cognitive impairment. Methods: The study included 32 HD patients and 30 age- and gender-matched controls. The demographic and clinical profiles of the patients were recorded. All subjects were evaluated by TMS and resting motor threshold (RMT), central motor conduction time (CMCT), silent period (SP), short-interval intracortical inhibition (SICI), and intracortical facilitation were determined. A battery of neuropsychological tests was administered to all subjects. Results: The mean age of the patients was 42.1 ± 14.1 years, and that of controls 39.4 ± 12.4 years (p = 0.61). There was no significant difference in RMT and CMCT between the two groups. There was a mild prolongation of the contralateral SP in HD, but it was not significant. SICI was significantly reduced in HD (p < 0.0001). A significant impairment in attention, verbal fluency, executive function, visuospatial function, learning, and memory was observed in HD patients. However, there was no correlation between cortical excitability changes and cognitive impairment. Conclusions: TMS is a valuable method of evaluating cortical excitability changes in HD. These patients have reduced SICI and significant impairment of cognition in multiple domains.

RÉSUMÉ: Évaluation des fonctions cognitives et de l’excitabilité des zones corticales chez des patients atteints de la maladie de Huntington. Contexte: Des progrès récents dans les techniques neurophysiologiques nous ont permis de mieux comprendre la physiopathologie de la maladie de Huntington (MH). Des études portant sur l’excitabilité des zones corticales motrices et sur les voies centrales motrices ont toutefois débouché sur des résultats variables. Objectifs: C’est au moyen de la stimulation magnétique transcrânienne (SMT) que nous avons cherché, en ce qui regarde la MH, à évaluer les variations de l’excitabilité des zones corticales. Nous avons aussi cherché à établir une corrélation entre ces variations et une dégradation des facultés cognitives. Méthodes: Notre étude a inclus 32 patients atteints de la MH et 30 témoins appariés selon l’âge et le sexe. Les profils démographiques et cliniques des patients ont été ensuite consignés. Tous les sujets de l’étude ont été évalués au moyen de la SMT ; ont été déterminés les seuils moteur au repos (SMR), les temps de conduction centrale (TCC), les intervalles de silence électro-cérébral, les processus d’inhibition intra-corticale à court intervalle ainsi que les processus de facilitation intra-corticale. Une série de tests neuropsychologiques ont également été administrés à tous les sujets de l’étude. Résultats: L’âge moyen des patients était de 42.1 ± 14.1 ans ; celui des témoins, 39.4 ± 12.4 ans (p = 0.61). Aucune différence notable n’a été observée entre ces deux groupes quant aux SMR et aux TCC. Un allongement modéré de l’intervalle controlatéral de silence électro-cérébral a aussi été noté dans le cas de la MH mais il ne s’est pas avéré significatif. Les résultats en matière de processus d’inhibition intra-corticale à court intervalle ont été réduits de façon importante dans le cas de la MH (p < 0.0001). Ajoutons qu’une dégradation cognitive importante a été rapportée chez les patients atteints de la MH, et ce, pour plusieurs fonctions : l’attention, la fluidité verbale, l’exécution de tâches, l’exploration visuo-spatiale, l’apprentissage et la mémoire. Cela dit, aucune corrélation n’a pu être établie entre des variations de l’excitabilité des zones corticales et une dégradation des facultés cognitives. Conclusions: La SMT constitue une méthode utile pour évaluer les variations de l’excitabilité des zones corticales dans le cas de patients atteints de la MH. Ces derniers ont donné à voir des processus d’inhibition intra-corticale à court intervalle réduits ainsi qu’une dégradation importante de nombreuses fonctions cognitives.

Keywords: Huntington’s disease, Transcranial magnetic stimulation, Neuropsychology, Motor threshold, Silent period, Paired stimulation
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INTRODUCTION

Huntington’s disease (HD) is an autosomal dominant chronic progressive neurodegenerative disorder due to abnormal expansion of CAG (cytosine–adenine–guanine) trinucleotide repeats in the Huntingtin gene (HTT) located on chromosome 4p that codes for the protein huntingtin.1 Although the exact biological functions of huntingtin is not fully understood, intracellular aggregates of this protein leads to mitochondrial dysfunction, with generation of reactive oxygen species, ATP depletion, and oxidative damage resulting in cell death.2 In addition to involuntary movements in the form of chorea, patients with HD may also present with several behavioral symptoms, including depression, mood disorders, psychosis, and cognitive impairment.3,4 The pathologic process

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involves selective loss of GABAergic neurons of the striatum with initial involvement of caudate and later putamen that results in reduced inhibition of the thalamus and overstimulation of the cerebral cortex through the excitatory glutamnergic projections.

Previous studies have shown cognitive decline in various stages of the disease as well as in the prodrome, years before the onset of motor symptoms. The impairment is seen on tests of attention, verbal fluency, psychomotor speed, executive functioning, learning and memory, emotional processing, and visuospatial functioning. Long-term memory is spared until late in the illness.

There is a growing interest in understanding the behavioral and cognitive changes in HD patients for several reasons. These behavioral and cognitive abnormalities impose a great burden on caregivers and families, and demonstrate disease-specific volume loss on MRI. As a result, studies of cognition in HD are emerging exponentially in order to develop valid and reliable measures of cognition in the prodromal as well as later stages.

Transcranial magnetic stimulation (TMS) is a noninvasive tool to evaluate the integrity of neural circuitry, and any abnormality may suggest neurotransmitter abnormalities in HD, which in turn may reflect the basis for motor and cognitive impairment in specific domains. TMS-based studies in patients with HD have yielded conflicting results, and hence the alterations in the neural circuitry in these patients has not been fully understood.

We therefore undertook this study to evaluate the cortical excitability changes using TMS and to understand the pathophysiological mechanisms underlying the disease. The other objective was to correlate the cortical excitability changes with cognitive dysfunction.

METHODS

Subjects

The prospective study was conducted in the Department of Neurology at the National Institute of Mental Health and Neurosciences in Bangalore, India, and was approved by its ethics committee. Thirty-two consecutive HD patients aged more than 18 and 30 age- and gender-matched healthy volunteers who gave written informed consent after having the nature and design of the study explained to them were included in the study. Subjects with a history of seizure, metallic implants in their body, cardiac pacemakers, and cochlear implants were excluded. All patients were clinically examined by a senior movement disorder specialist (PKP) and severity of the motor symptoms was scored using the motor part of the Unified Huntington Disease Rating Scale (UHDRS).

Genetic testing was performed in all patients in order to confirm the diagnosis of HD. CAG repeat length (from region 5 of the HTT gene) was determined after polymerase chain reaction amplification of genomic DNA obtained from the peripheral blood of HD patients.

Both patients and controls underwent TMS and neuropsychological tests. Medications that can affect cortical excitability changes (e.g., benzodiazepines, carbamazepine, tetrabenzine) were stopped a week prior to these tests.

TMS Methodology

TMS was administered using two Magstim-200 stimulators connected through a bistim module. Subjects were allowed to sit comfortably on a chair, and magnetic stimuli were given using a handheld figure-of-eight coil with an inner diameter of 70 mm over the left primary motor cortex, and responses were recorded from the right first dorsal interosseus (FDI) muscle using Ag–AgCl surface electrodes arranged in a belly-tendon montage. The stimulus intensity was increased in a stepwise manner until a satisfactory motor-evoked potential (MEP) was obtained. The area of optimal MEP (hotspot) was marked over the scalp, and subsequently the coil was positioned on the same area at an angle of 45° pointing backward, and was evaluated for resting motor threshold (RMT), central motor conduction time (CMCT), silent period (SP), short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF).

RMT was defined as the minimum stimulus intensity required to evoke peak-to-peak MEPs from a relaxed FDI to a minimum 50 µV peak-to-peak in at least 5 out of 10 trials. Stimulus was given only after ensuring complete relaxation of the muscle under audiovisual guidance. In order to determine the CMCT, MEPs were recorded using 120% of the RMT. The CMCT was then calculated using the F-wave method. F-waves were recorded from the FDI after electrically stimulating the right ulnar nerve at the wrist with a supramaximal stimulus. A total of 20 recordings were taken, and the F-wave latency was measured. The CMCT was calculated using the formula

\[
\text{CMCT} = \text{MEP} - \frac{(F + M - 1)}{2},
\]

where MEP is the MEP latency, F is the F-wave latency, and M is the M-wave latency. The contralateral SP (cSP) was recorded from the partially contracted right FDI muscle (30% of maximal contraction) with a stimulus intensity of 120% of the RMT under audiovisual feedback to ensure the same amount of muscle contraction during each stimulus.

In a paired stimulation study, an initial conditioning stimulus (CS) that is subthreshold (80% of the RMT) was given followed by a second test stimulus (TS) at a suprathreshold level (120% of the RMT). The interval between the TS and CS, known as the inter-stimulus interval (ISI), was fixed at 3 and 10 ms. The recording included three conditions: a single-pulse TMS at 120% of the RMT, a paired pulse with a 3-ms ISI, and a paired pulse with a 10-ms ISI. Ten responses were obtained for each of the conditions. The mean amplitude of the MEP obtained after paired stimulation at each ISI was expressed as the ratio of the mean amplitude obtained by paired stimulus (CS + TS) to unconditioned TS (single-pulse TMS). The response obtained at an ISI of 3 ms was documented as SICI, and that obtained at 10 ms was documented as ICF.

Neuropsychological Battery

Cognitive assessment was done in both patients and controls using a battery of selected neuropsychological tests that included the Mini-Mental Status Examination (MMSE), a frontal assessment battery (FAB), the Montreal Cognitive Assessment (MoCA, v. 7.1; www.mocatest.org), digit span forward and backward, a verbal fluency test (controlled word-association test and animal-naming test), the Corsi block-tapping test, response inhibition (the Stroop test), Rey’s auditory verbal and learning test (AVLT), and a validated story recall test. These tests were done prior to administration of TMS.

Statistical Analysis

Statistical analysis was carried out using R software. Data were expressed using descriptive statistics (e.g., for continuous
variables, means and standard deviations; and for categorical variables, frequency and percentage). Comparison between continuous variables was done using an independent Student’s t test and a chi-square test for categorical variables. Correlation between continuous variables was done using Pearson’s correlation coefficient. A value of $p < 0.05$ was considered statistically significant.

**RESULTS**

**Demography and Clinical Characteristics (see Table 1)**

Some 32 HD patients (12 women and 20 men) and 30 controls (13 women and 17 men) were included in our study. The mean age of patients was 42.1 ± 14.1 years and that of controls 39.4 ± 12.4 years ($p = 0.61$). The mean UHDRS score was 36.4 ± 11.0 years, range 25-58 years; women 36.6 ± 10.9 years, range 20-54 years). The mean UHDRS score was 36.4 ± 13.3, with a range between 15 and 78. The mean CAG repeat length was 45.2 ± 17.8 (range 13-112). The mean age at onset of symptoms was 38.5 ± 10.9 years, with a range of 20-58 years (men 39.8 ± 11.0 years, range 25-58 years; women 36.6 ± 10.9 years, range 20-54 years). The mean UHDRS score was 36.4 ± 13.3, with a range between 15 and 78. The mean CAG repeat length was 45.2 ± 6.1 (range = 40-73).

**TMS parameters (see Table 2)**

**Single-Pulse Stimulation**

The RMT in patients was 36.6 ± 12.3% and that in controls 33.2 ± 5.7% ($p = 0.17$). The CMCT in patients was 7.8 ± 2.2 ms and in controls 7.3 ± 2.0 ms ($p = 0.38$). Prolongation of the cSP was observed in HD patients at 97.9 ± 51.0 ms in comparison to controls (80.1 ± 23.3 ms), but the difference was not significant ($p = 0.09$).

**Paired Stimulation**

SICI and ICF were measured as a ratio of the MEP amplitude obtained after combined CS and TS to TS alone (CS + TS/TS). A ratio of more than 1 suggests enhancement of MEP (ICF) and less than 1 suppression of MEP (SICI). At an ISI of 3 ms, the change in MEP amplitude in patients was 1.64 ± 1.3 compared to 51.0 ± 80.1 ms, but the difference was not significant ($p = 0.09$).

**Correlation of TMS Parameters with UHDRS Score, CAG Repeat Length, and Disease Duration**

Correlation analysis was carried out between TMS parameters and such disease parameters as CAG repeat length and UHDRS motor scores. None of them showed any significant correlation

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**Table 1: Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (women/men)</td>
<td>12/20</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>42.1 ± 14.1 years</td>
<td></td>
</tr>
<tr>
<td>Age at onset (mean ± SD)</td>
<td>38.5 ± 10.9 years</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (mean ± SD)</td>
<td>48.4 ± 24.6 months</td>
<td></td>
</tr>
<tr>
<td>CAG repeat length (mean ± SD)</td>
<td>45.2 ± 6.1</td>
<td></td>
</tr>
<tr>
<td>UHDRS score (mean ± SD)</td>
<td>36.4 ± 13.3</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Comparison of TMS parameters between cases and controls**

<table>
<thead>
<tr>
<th>TMS Parameters</th>
<th>Patients (32)</th>
<th>Controls (30)</th>
<th>Value of $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMT (%)</td>
<td>36.6 ± 12.3</td>
<td>33.2 ± 5.7</td>
<td>0.17</td>
</tr>
<tr>
<td>CMCT (ms)</td>
<td>7.8 ± 2.2</td>
<td>7.3 ± 2.0</td>
<td>0.38</td>
</tr>
<tr>
<td>Contralateral SP (ms)</td>
<td>97.9 ± 51.0</td>
<td>80.1 ± 23.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Spinal SICI (CS–TS/TS)</td>
<td>1.64 ± 1.3</td>
<td>0.56 ± 0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICF (CS–TS/TS)</td>
<td>2.16 ± 1.61</td>
<td>2.7 ± 1.16</td>
<td>0.15</td>
</tr>
</tbody>
</table>

CMCT = central motor conduction time; CS = conditioning stimulus; ICF = intracortical facilitation; RMT = resting motor threshold; SICI = short-interval intracortical inhibition; SP = silent period; TS = test stimulus.

**Table 3: Neuropsychological assessment of subjects**

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Patients (n = 32)</th>
<th>Controls (n = 30)</th>
<th>Value of $p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>24.9 ± 4.3</td>
<td>29.6 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MoCA</td>
<td>22.9 ± 4.6</td>
<td>29.4 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FAB</td>
<td>11.2 ± 3.0</td>
<td>17.6 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Animal naming test</td>
<td>9.8 ± 3.7</td>
<td>14.4 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2. FAS battery</td>
<td>8.8 ± 3.1</td>
<td>26.6 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digit span forward</td>
<td>5.1 ± 0.9</td>
<td>6.7 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>3.4 ± 0.7</td>
<td>4.8 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corsi span forward</td>
<td>4.7 ± 1.0</td>
<td>6.0 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Story recall (immediate)</td>
<td>9.6 ± 3.2</td>
<td>13.3 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Story recall (delayed)</td>
<td>7.9 ± 3.0</td>
<td>11.9 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroop effect (seconds)</td>
<td>161.8 ± 78.6</td>
<td>95 ± 12.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>

MoCA = Montreal Cognitive Assessment; RAVLT = Rey’ Auditory Verbal and learning test.
The duration of the SP has also been shown to have clinical significance. Prolonged SP has been described in other patients and controls. There are studies that have shown agreement with the work of several other researchers who did not identify that predict the time to diagnosis, suggesting that these are important markers of prognosis. Studies have shown that SICI is GABA\(_A\)-mediated. A reduction in the GABA\(_A\) system causes reduced SICI, and overexpression of the glutaminergic system enhances ICF. This alteration in monoamine concentrations results in a change in the pattern of the excitability of neurons. The facilitatory neurons become more susceptible to stimulation as compared to inhibitory neurons. However, this was not observed in some recent studies. Paired transcranial stimulation is a more sensitive measure in detecting changes of cortical excitation levels than single stimulation.

A comparison of our present study with previous studies is provided in Table 4.

**Cognition in HD**

The HD patients in our study had significant impairment on the neuropsychological tests, suggesting involvement of attention, memory, learning, visuospatial abilities, and executive functions. As with other neuropsychiatric disorders, the presentation of HD varies considerably between individuals. Some individuals present with more noticeable motor dysfunction, whereas others present primarily with cognitive or psychiatric disturbances. The FAB has been used to evaluate executive function in HD. In a study of 41 HD patients and 53 controls, FAB scores were lower in patients than in the controls (p < 0.001). It also helped in differentiating between HD patients in the initial and later stages of the disease. This one-year longitudinal evaluation revealed a global trend toward a worsening in the second score on the FAB. In the PREDICT–HD study, out of the 18 tests applied, 6 were identified that predict the time to diagnosis, suggesting that these are important markers of prognosis.

In a study of 54 at-risk HD patients, abnormal semantic fluency and visual discrimination learning was noted. Abnormality was
Relationship between Cortical Excitability Changes and Cognitive Impairment

Though we did not find any correlation between the two, it appears that these changes occur in parallel, as evidenced by the significant difference between HD patients and controls in cognitive testing and SICI. Further studies are required to address this issue.

LIMITATIONS OF THE STUDY

Ipsilateral SP was not tested in our patients, as most had difficulty in fully contracting the FDI muscle, and they could also not tolerate the stimulus intensity, which is 100% of stimulator output. Recording of ipsilateral SP could have contributed to the callosal function in HD patients.

CONCLUSIONS

TMS is a valuable method of evaluating the cortical excitability and central motor pathways in patients with HD. There is reduced SICI, as evidenced by paired stimulation research. Our study has tried to look into the cognitive impairment in HD patients using a battery of nine neuropsychological tests and has found profound impairment in attention, memory, and visuospatial and executive functioning. A comprehensive and sensitive neuropsychological battery to assess cognition in HD is still lacking. Such a battery is required to evaluate outcome, and to predict and track disease progression. It would also be useful in formulating appropriate therapeutic strategies and guidelines for management of the disease. There is also a need for further studies to understand cortical excitability changes and intracortical inhibition, as previous studies have yielded variable results.

DISCLOSURES

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