Sensation of effort is altered in Huntington’s disease

Gilles Lafargue, Angela Sirigu

Institut des Sciences Cognitives, CNRS, 67 Boulevard Pinel, 69675 Bron, France

Received 7 May 2001; received in revised form 10 January 2002; accepted 28 January 2002

Abstract

In this study, we investigated sensation of effort in Huntington disease (HD). We tested the hypothesis that the basal ganglia are involved in processing effort sensation. The experimental paradigm consisted in a contralateral matching procedure where normal subjects (N = 6) and HD patients (N = 6) were required to lift a reference weight with their non-dominant index, and then compare the target-weight with variable weights lifted by the dominant index. Two kinds of sequences were administered: (1) increasing, where the first weight was lighter than the reference weight and progressively increased in 20 g steps, (2) decreasing, where trials started with a heavier weight and progressively decreased. We calculated the discrimination threshold (DT) across sequences as the weight for which the subject’s response changed sign. The difference between the higher and the lower threshold was defined as “uncertain area”. We predicted that controls should overestimate the reference weight lifted by their non-dominant hand because the same effort produces more force when applied to stronger muscles. If the basal ganglia mediates sensation of effort, patients’ capability to discriminate weights should be degraded. As expected, normal subjects overestimated the reference weight lifted by their non-dominant index and showed a restricted uncertain area, thus, indicating that were able to discriminate minimal differences in generated forces. By contrast, patients with HD underestimated the reference weight lifted by their non-dominant hand and showed a broad uncertain area, thus, demonstrating that they could detect only important differences in the matched efforts. These results suggest that effort sensation critically involves the basal ganglia. In normal conditions, in parallel with the efferent command of force, an efferent copy reflecting the magnitude of the voluntary motor command is transmitted to sensory centres. This signal and/or the integration of sensory feedback which generates what is experienced as the sense of effort, would be altered in HD. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Huntington disease (HD); Sensation of effort; Basal ganglia

1. Introduction

Effort sensation can be defined as “how hard one tries when carrying out a motor task” [6]. This component of the motor representation, that we will explore in the present study, seems to have a central origin. Psychophysical studies examining the nature of the sensory systems mediating the perceived amplitude of forces and weights suggest that sensation of effort is not directly derived from the peripheral feedback arising from skin, joints and muscles receptors. The hypothesis that feeling of effort has a central origin is based on at least three arguments. First, it has been observed that in normal subjects a weight lifted by weakened muscles is perceived as heavy. This perception occurs whether the weakness is caused by partial curarisation [12,13] or muscular fatigue [14,37]. These results suggest that subjects produce more force centrally to overcome a local muscles weakness. Therefore, increasing effort sensation should be the subjective counterpart of the increasing central command of force. This behaviour has also been described in patients with capsular stroke [48] or in the case of cerebellar lesion [2,12,29]. The second argument in favour of a centrally-mediated sense of effort comes from results which show that effort is not experienced when peripheral receptors are passively excited [22,37]. In contrast, effort can be experienced when the subject is simply imagining a movement [11] or observing somebody else doing an effortful action [42]. Moreover, sensation of effort is preserved following peripheral deafferentation [36,51]. For instance, Rothwell et al. [51] described the case of a patient suffering from sensory neuropathy, who was unable, without visual feedback, to estimate the weight of an object placed in his hand because “he did not know when the weight had been lifted” [51]. However, his ability to match a constant force applied to one thumb with a variable force applied to the other thumb was comparable to that of normal individuals, if he was given a slight indication of thumb movement. Such a performance in a deafferented subject seems to be the result of an accurate sense of effort [33]. Third, sensation of effort is not abolished after clinically complete transaction of the spinal cord.
at or below the mid-cervical level, when subjects attempt to contract the paralysed muscles below the lesion level [15,28]. Although the role of afferent inputs to the awareness of effort does not seem crucial, their contribution, however, must not be dismissed. Information arising from Golgi tendon organs are required to provide a signal that the force generated by the muscles is adequate to the task requirements [14]. Moreover, reflex inputs from joints muscles and skin receptors can inhibit or facilitate motoneurons in the spinal cord and in doing so, they may have an influence on the magnitude of the centrally generated motor command, and, hence, on the perception of the generated effort. For example, a study by Kilbreath et al. [35] using a bilateral weight-matching paradigm, showed that perceived heaviness during anaesthesia differed in magnitude for the different digits. Anaesthesia of the thumb and index finger produced increases in perceived heaviness while anaesthesia of the ring and the little finger decreases perceived heaviness. The authors suggested that heaviness is biased by signals of motor commands. Thus, the role of afferent inputs might not be to generate the signal of effort but rather to calibrate and modulate this sensation.

Where in the CNS this signal is read off remains unclear. The feeling of effort is probably generated in the motor path. For example, hemiplegic patients reported that attempts to move the paralysed limb produce no sensation of effort [7,38,48]. Moreover, passive movements elicited by intracortical electrical [43] or magnetic [18] stimulation in the primary motor cortex are not associated with sensation of effort. A projection to (or from) the primary motor cortex might be essential for the generation of the effort signal [16]. Because of the anatomical and functional link with the frontal cortex, it has been suggested that basal ganglia may be involved in the mediation of this process [16,31]. This hypothesis has recently been supported by Romero et al.’s results [49] in which healthy subjects were required to produce, through motor imagery, two isometric force levels. The authors showed that variations in target-forces (TFs) was associated with specific variations in even-related potentials pattern in the supplementary motor area (SMA). As input to the SMA arises predominantly from the globus pallidus, via the ventral lateral thalamus [30], deficits in perceived effort would be expected in Huntington disease (HD).

In the present study, we tested this hypothesis by investigating sensation of effort in patients affected by HD. HD disease is a degenerative disorder which provides an interesting model to assess the nature and the neural bases of the sense of effort. At the neuropathological level, the early stage of the disease is characterised by a selective degeneration of striatal neurons with a relative sparing of the nigrostriatal tract and dopaminergic nerve cells [9]. At the behavioral level, chorea is the most important feature of HD, although it is only one part of a generalised motor disturbance, which also includes bradykinesia, i.e. an abnormal slowing of voluntary movements [20,21,45]. Previous studies have shown that when compared to age-matched healthy subjects, HD patients have reduced movement speed [26]. Movement slowness is particularly manifest in tasks involving sequential movements [2,44,58]. Although, HD has been generally considered as equally affecting both the left and right side of the body, some authors reported that patients with HD have specific difficulties when initiating movements with their non-preferred hand (the left in right-handers) [4,19]. Furthermore, the asymmetry in striatal volume as described in normal subjects, the left striatum larger than the right [47], seem to be reversed in HD [50]. If the relevant discharges for sensation of effort are relayed by the basal ganglia [16] and if this sensation is derived from an efferent copy of the central command of force, a dissociation between the magnitude of the command (the original signal) and the magnitude of the sensation of effort (the copy) might be observed when a lesion occurs in this cerebral structure. Moreover, if the non-dominant hand inferiority in HD [4] reflects asymmetrical lesions within the striatum [50], sensation of effort, like movement initiation, should be more-affected when associated with left-hand force production. We examined this issue by using a contralateral matching procedure [37]. In such a procedure the forces exerted by a group of muscles in one limb, designated the reference limb, are matched for subjective magnitude, with the corresponding group of muscles in the other limb. In our study, normal controls (NCs) and HD patients were first required to lift a reference weight with their non-dominant (left) index, and to concentrate on the felt sensation. Second, they were asked to compare the target-weight, on the basis of the felt sensation, with variable weights lifted by the dominant (right) index.

We predicted that controls should overestimate the reference weight lifted by their non-dominant index because the same effort produces more force when applied to stronger muscles. The patients’ general ability to discriminate weights should be degraded and, in contrast with controls’ performance, they should underestimate the reference weight lifted by their non-dominant (more-affected) hand.

2. Materials and methods

2.1. Subjects

Six patients (five females and one male) with HD disease and six NCs with no history of neurological disorders were studied. The two group of subjects were matched for age (HD: 41.9 years, range 35–50; NCs: 44.5 years, range 33–52) and educational level (HD: 10.6 years more or less 1.5; NCs: 11 years more or less 1.8) (Table 1). NCs and patients handedness was investigated by using a questionnaire were subjects answered queries (N = 10) about their hand preference for different daily life activities such as drawing, throwing, using hammer, using scissors, etc. Both patients
can be lifted with a single finger. The resistance could be
The extremity of each rod ends with a small sphere which
gravimeter composed of two horizontal, parallel and identi-
2.2. Procedure
by Harris et al. [25] age-onset [25]. Using the regression equation, as provided
duction in the volume of the putamen and, to a lesser de-
reason of his inclusion is because of the estimated prox-
clinical characteristics of Huntington patients
Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Time since onset (years)</th>
<th>Education</th>
<th>Stage</th>
<th>Mattis</th>
<th>Chorea (0–3)</th>
<th>Number of targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>F</td>
<td>2</td>
<td>10</td>
<td>2/5</td>
<td>126</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>2</td>
<td>9</td>
<td>1/5</td>
<td>128</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>F</td>
<td>1</td>
<td>9</td>
<td>1/5</td>
<td>130</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>F</td>
<td>1</td>
<td>14</td>
<td>1/5</td>
<td>143</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>F</td>
<td>3</td>
<td>12</td>
<td>2/5</td>
<td>135</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>F</td>
<td>2</td>
<td>10</td>
<td>1/5</td>
<td>133</td>
<td>1</td>
<td>47</td>
</tr>
</tbody>
</table>

*Pre: pre-symptomatic.

and normal subjects were found strongly right-handed. An
Sensation of effort was measured using a Pieron's
The reference weight was fixed in our experiment at 280 g
for daily
2.3. Data analysis
At the end of each sequence, an instantaneous discrimi-
threshold (DT) of effort sensation was obtained. This
threshold corresponds to the weight for which the subject’s
response changed sign. The averages of thresholds of the
increasing and the decreasing sequences provide two thresh-
holds: a higher and a lower. The difference between these
two thresholds is called “uncertain area” where subjects'
ability to discriminate the reference weight is at chance,
that is, the variable weights lifted by the matching hand are
do not discriminated from the reference weight lifted by the
reference hand: subjects say “larger” in 50% of the cases
and “lower in 50% of the cases. Finally, a point of subjec-
tive equality (PSE) was calculated for each subject: PSE =
(inferior threshold + superior threshold)/2.
3. Results

3.1. Higher and lower discrimination thresholds

The average of lower thresholds (95.2% of the reference weight) was different from the average of higher thresholds (105.4% of the reference weight) ($F(1, 10) = 16.04; P < 0.01$) (Fig. 1). This main effect can be explained by the interaction between DT and group ($F(1, 10) = 8.78; P < 0.01$). The difference between lower and higher thresholds was small (2.6%) in controls. This difference was much more important (17.8%) in HD (Fig. 1). The area separating lower from higher thresholds has been defined as “uncertain area”. Individual data illustrated in Fig. 2 shows that the area of uncertainty for control subjects is smaller and located above 100% reference weight, thus, indicating a tendency to overestimate it. In contrast, patients’ uncertain area is large and generally located below 100% of the reference weight, thus, indicating a tendency to underestimate it.

3.2. Point of subjective equality

In the control group, the matched effort sensations between the two hands result in a over-estimation of the reference force (the one produced with the left index). The PSE (centre of the uncertain area, obtained with the index of the right-dominant hand) was, on average, heavier by 7.2% than the reference weight. On the other hand, HD patients, underestimated the reference weight lifted with their non-dominant index. They behaved as if they were matching a weight 6.6% lighter than the one lifted with the right less affected-index. The difference between controls and HD patients (13.8%) is significant ($F(1, 10) = 25.78; P < 0.001$) (see Fig. 1).

4. Discussion

The purpose of this study was to test the hypothesis that sensation of effort critically involves the frontostriatal system and that this sensation is derived from an efferent copy of the central command of force. To this end, we used a contralateral matching procedure with a Pieron’s gravimeter. This is an objective method to quantify the magnitude of
effort sensation [18,35,37]. In such a paradigm, the sensation perceived when a given force is developed on one side, is compared with the felt sensation when another force is developed by the other side.

In accordance with our expectations, the control subjects over-estimated the reference weight lifted by the index of their non-dominant hand. This result fits with what can be experienced in every day life and is consistent with the idea that subjects compared the two produced forces on the basis of a central signal. Indeed, a given force requires more effort when produced with the non-dominant hand than when produced with the dominant one: in order to feel the same sensation of effort in both sides subjects have to produce more force with the dominant hand as compared to the one produced with the non-dominant one. Hence, because of the relative weakness of the left-hand in right-handed subjects, our data is in agreement with the results obtained by Henningsen et al. [27]. In this study, the authors using a bilateral matching task, showed that normal subjects produced larger isometric forces with the dominant index when compared to the non-dominant one: in order to feel the same sensation when another force is developed with the non-dominant hand than when produced with the dominant one, a TF of 200g. The same subjects also had higher maximum finger flexion forces with their right-dominant index. In our study, in addition to target-weight overestimation, NCs “uncertain area” was small, thus, indicating that subjects were able to discriminate minimal increasing or minimal decreasing weights, solely on the basis of the sensation of effort.

Compared to controls, patients with early HD showed, in average, greater forces in the right than in the left side. Our data in agreement with the results obtained by Henningsen et al. [27]. In this study, the authors using a bilateral matching task, showed that normal subjects produced larger isometric forces with the dominant index when compared to the non-dominant one: in order to feel the same sensation when another force is developed with the non-dominant hand than when produced with the dominant one, a TF of 200g. The same subjects also had higher maximum finger flexion forces with their right-dominant index. In our study, in addition to target-weight overestimation, NCs “uncertain area” was small, thus, indicating that subjects were able to discriminate minimal increasing or minimal decreasing weights, solely on the basis of the sensation of effort.

In accordance with our expectations, the control subjects over-estimated the reference weight lifted by the index of their non-dominant hand. This result fits with what can be experienced in every day life and is consistent with the idea that subjects compared the two produced forces on the basis of a central signal. Indeed, a given force requires more effort when produced with the non-dominant hand than when produced with the dominant one: in order to feel the same sensation of effort in both sides subjects have to produce more force with the dominant hand as compared to the one produced with the non-dominant one. Hence, because of the relative weakness of the left-hand in right-handed subjects, our data is in agreement with the results obtained by Henningsen et al. [27]. In this study, the authors using a bilateral matching task, showed that normal subjects produced larger isometric forces with the dominant index when compared to the non-dominant one: in order to feel the same sensation when another force is developed with the non-dominant hand than when produced with the dominant one, a TF of 200g. The same subjects also had higher maximum finger flexion forces with their right-dominant index. In our study, in addition to target-weight overestimation, NCs “uncertain area” was small, thus, indicating that subjects were able to discriminate minimal increasing or minimal decreasing weights, solely on the basis of the sensation of effort.

Compared to controls, patients with early HD showed, in average, larger “uncertain area”, thus, demonstrating that they could detect the change in sign only for more important increasing or decreasing weights. In addition, they systematically underestimated the reference weight lifted by their weaker left-hand. The main performance we found in HD patients is clearly different not only from that of normal subjects but also from the behaviour described in the literature following damage to other cerebral structures. This result supports the hypothesis of an altered effort perception in HD. As mentioned in Section 1, a force produced by weakened muscles is overestimated in a variety of conditions: in normals, when the weaknesses is due to fatigue [14,32,37] or partial curarisation [12,13], in patients, in the case of unilateral cerebellar lesion [2,12,29] or in the case of unilateral capsular stroke [48]. So, the question arises of why HD patients do not overestimate a weight lifted by their weaker left-hand even more than normal subjects?

A first possibility is that the left index finger of our patients was not the weakest. However, this does not appear reasonable because, as reported by other studies, the normal manual asymmetry between left and right-hand is exacerbated in HD [4,19]. When force strength was clinically tested in our patients this left-hand inferiority was also found. Thus, if anything, we should have observed an even larger overestimation of the weight lifted by the non-dominant hand than in normal subjects.

Alternatively, our results can be explained by a selective impairment in the sense of effort in HD. This impairment could have two different sources. Firstly, effort is derived from feed-forward information. In normal conditions, in parallel with the efferent command of force, an efferent copy reflecting the magnitude of the voluntary motor command is transmitted to sensory centres. This signal would be selectively altered in HD. HD patients should still be able to programme a given force, but they should not feel the adequate associated sensation. Secondly, efferent copy probably interacts with afferent information before gaining access to consciousness. Afferent inputs arising from Golgi tendon organs, skin receptors and muscle spindles may calibrate the central signal of effort [16,17]. Thus, we may suppose that integration of afferent signals, and not corollary discharge of the central motor command per se, is affected in HD. It is difficult to separate the two alternative interpretations. To our knowledge, however, basic somatosensory disturbances in HD, particularly during the early stage of the disease, have not been described. In a quasi-static condition, HD patients are able to scale grip force appropriately to the object weight or texture [23], indicating that sensory adaptation occurs with the physical properties of the manipulated object. Nevertheless, there have been reports of abnormal somatosensory cortex activation during passive sensory stimulation [5] and changes in somatosensory-evoked potentials (S5) when external perturbations are introduced during reaching movements [41,59]. Based on this evidence, we can assume that sensory deficits may provoke more random decisions in our weight-matching task and accordingly be the cause of the increased “uncertain area” we observed in our patients. Such a possibility, however, seems unlikely to account for HD performance because in normal subjects with anaesthetised digits, there is no significant difference in the reproducibility of the estimates of perceived heaviness between non-anaesthetised and anaesthetised conditions [35]. Furthermore, recent data obtained in two severely deafferented patients following peripheral injury (Lafargue et al., submitted) show that these patients are able to accurately discriminate isometric forces solely on the basis of internal signals.

Lastly, because HD is not only characterised by motor impairments but also by cognitive deterioration [8], it is tempting to argue that the observed deficit in matching efforts is the result of a disorder in decision making or the consequence of a general intellectual decline. It is known that the prefrontal cortex is involved in decision processes [52] and this structure receives dense projections from the caudate nucleus [1]. So, can the deficit we observed in HD be ascribed to a general cognitive impairment? We think the answer is no and for the following arguments. First, there was no correlation between patients’ mental status and discrimination capabilities. For instance, patient 1 who obtained the worse score in the Mattis scale, underestimated the reference weight although he exhibited an uncertain area similar to that of his age-matched control, thus, suggesting...
that perceived effort changed (less intense) but was still relatively well graded and accurate. Such a dissociation between change in perceived heaviness and preserved discrimination capability has already been described after anaesthesia of the digits [35]. Second, a general discrimination disorder might have produced a more random performance. On the contrary, HD patients consistently underestimated the weight matched by their non-dominant hand. As trials were given in increasing and decreasing blocks, the homogeneity of HD's performance suggest that they are not responding at chance. Finally, note that patient 4, who was HD gene carrier, but did not show clear signs to confirm a clinical diagnosis of HD, also underestimated the reference weight. Further work must determine if perception of muscular effort, as movement jerkiness [55], is a sensitive indicator of presymptomatic HD progression.

Interestingly, Nordin et al. [40] reported that HD were selectively impaired in discriminating odours. When compared to controls, patients showed a significant difference in Weber ratio, for odour, but not for taste, thus, suggesting that if any high-level cognitive difficulty underlie patients' performances this, would also be reflected in taste thresholds. Similarly to the poor performances as reported by Nordin et al. [40], for olfactory discrimination, it seems reasonable to argue that the decline in effort sensation observed in the present study, is modality-specific and cannot be accounted by a general cognitive problem.

Basal ganglia project in the frontal lobe with at least five segregated loops [1]. The selective deficit in olfactory processing in HD observed by Nordin et al. [40] has been attributed to the dysfunction of the orbitofrontal loop. This loop, interconnecting orbitofrontal cortex, basal ganglia and thalamus [1], is indeed involved in processing olfactory information [46]. Another anatomically and functionally independent loop, the motor one, described by Alexander et al. [1] might be involved in mediating sensation of effort. The motor loop, which is impaired in HD [3,60], interconnects SMA, putamen and thalamus. This loop may be also involved in processing sensation of effort. In a recent study, Romero et al. [49] have shown that during mental imagery of isometric action, low and moderate force-productions were correlated with variation in event-related potentials patterns in SMA. As TF is considered a low-order movement parameter [34], the authors suggested that the ERP patterns observed in the SMA/PMA, may reveal “other movement characteristics associated with variation in TF, such as effort” [49]. Our results are consistent with this view. In HD, either basal ganglia dysfunction or SMA perturbation secondary to striatal lesions could induce deficits in perceived effort.

Although the early stages of HD, are currently regarded as a model of basal ganglia function, without measures of basal ganglia dysfunction against which the deficit we found can be correlated, we cannot confirm that the deficits observed in this study come from striatal dysfunction. Post-mortem studies have shown that HD patients exhibited cortical atrophy [24,56]. However, it is not yet established whether it is a primary phenomenon or the consequence of a loss of striatal input to cortical areas such as the parietal cortex. Functional imaging studies have reported a decreased activity in several cortical areas in HD [3,60]. However, at least three arguments let us suggest that is directly related to basal ganglia dysfunction: (i) a relatively similar pattern of cortical decrease in activation has also been observed in Parkinsonian patients [60], (ii) data from the experimental HD model in rats demonstrates that BG dysfunction alone induced cortical alteration similar to those observed in HD [53], (iii) Using the same experimental set-up, we are currently investigating sensation of effort after focal cortical lesions (Lafargue et al., in preparation). Preliminary observation in two patients with focal damage in the inferior parietal cortex shows that both patients performed well in this task. This was not the case for a patient with a selective lesion in the premotor region whose area of uncertainty was significantly larger compared to control performance.

Our data might be confirmed in patients with unilateral focal basal ganglia lesions in different conditions of force production (i.e. isometric, anisometric). If further studies confirm the idea that effort sensation is processed in the basal ganglia, a future step will be to identify how feeling of effort is processed along the different cortical and subcortical regions involved in sensorimotor processing.

References


