Experimental Neurology 216 (2009) 148–157

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Alterations in voluntary movement execution in Huntington's disease are related to the dominant motor system — Evidence from event-related potentials

Christian Beste [a,b,*], Carsten Konrad [c], Carsten Saft [d], Tim Ukas [c], Jürgen Andrich [d], Bettina Pfleiderer [e], Markus Hausmann [f], Michael Falkenstein [a]

[a] Leibniz Research Centre for Working Environment and Human Factors, WHO Collaborating Centre for Occupational Health, Ardeystr. 67, D-44139, Dortmund, Germany
[b] Institute for Cognitive Neuroscience, Biopsychology, Ruhr-University Bochum, Germany
[c] Department of Psychiatry and Psychotherapy, Interdisciplinary Center for Clinical Research (IZKF), University of Münster, Germany
[d] Department of Neurology, Huntington Centre NRW, St. Josef-Hospital, Ruhr-University Bochum, Germany
[e] Department of Clinical Radiology, University of Münster, Germany
[f] Department of Psychology, Durham University, Durham, UK

ARTICLE INFO

Article history:
Received 29 October 2008
Revised 19 November 2008
Accepted 20 November 2008
Available online 10 December 2008

Keywords:
Huntington's disease
Voluntary movements
Event-related potential (ERP)

ABSTRACT

Huntington's disease is an autosomal dominant neurogenetic disorder leading to striatal atrophy, characterized by involuntary movements. Voluntary movements also deteriorate, but the neurophysiological mechanisms are less understood. We investigated voluntary movement execution and its neural correlates by means of movement-related potentials (MRPs) in symptomatic HD (HD), presymptomatic HD (pHD) and controls.

Reaction times (RTs) revealed hand differences in controls and HD, but not in pHDs. Response-locked MRPs above the contralateral primary motor area (M1) were similar across all groups. Yet, the HD-group showed, selectively for the right hand, a second contralateral (left) activation after the response, followed by similar activation over the ipsilateral (right) motor area, which is normally inhibited. Similarly parietal processes were reversed for right hand movements. In strong contrast, pHDs showed an increased inhibition of the ipsilateral hemisphere.

The results suggest modulations of inhibitory processes in HD dependent on disease stage. Importantly, these modulations occur after the response and are restricted to right-hand responses, or the dominant motor system (left hemisphere). Since also cognitive processes preceding the MRPs changed, the results suggest a cognitive contribution to the emergence of voluntary movement dysfunction. The pattern in the pHD-group, namely an increased inhibition of the ipsilateral hemisphere and similar RTs between the hands suggest compensatory mechanisms in presymptomatic stages of the disease. Despite neurophysiological alterations originating in the dominant left hemisphere in HDs, they also affect the right hemisphere, probably due to a dysfunction in interhemispheric inhibition in HD.

Introduction

Huntington's disease (HD) is an autosomal dominant neurological disorder. The causative mutation is an expansion of the CAG trinucleotide repeat in the HD gene (*IT 15*) on chromosome 4 (Beal and Ferrante, 2004). The most prominent sign of HD is chorea (Van Vugt et al., 1996; Penney et al., 1990). These motor symptoms are probably related to striatal pathology (e.g. Aylward et al., 2004; Kassubek et al., 2005; Thieben et al., 2002; rev. Rosas et al., 2004). The striatum can be seen as the main focus of pathology and is found to be more pronounced in the left hemisphere (Finke et al., 2006). Degeneration begins in the medium spiny neurons (MSN) (Cepeda et al., 2007) that provide inhibitory synaptic connections (Bevan et al., 2002) to pallidal structures. MSNs play an important role regulating the striatal output to pallidal structures (Gurney et al., 2004; Wickens and Wilson, 1998). Pallidal structures in turn project to the VA/VL complex of the thalamus, which in turn project to the primary motor cortex (Purves, 2004). Striatal and pallidal basal ganglia structures are influenced by the substantia nigra and the nucleus subthalamicus, respectively.

Thalamic structures are also affected in HD (Beste et al., 2008; Kassubek et al., 2005) and hence an important structure mediating voluntary movement is dysfunctional, too. Indeed, it has been shown that voluntary movements are affected in HD (Kremer, 2002), which greatly impairs everyday living (Van Vugt et al., 2004). Since the precise nature of this motor impairment in HD is unknown (Kremer, 2002) we try to elucidate these processes on a neurophysiological level by using event-related potentials (ERPs). The most frequently used movement-related ERP component, the lateralized readiness

* Corresponding author. Leibniz Research Centre for Working Environment and Human Factors, WHO Collaborating Centre for Occupational Health and Human Factors, Ardeystr. 67, D-44139 Dortmund, Germany. Fax: +49 231 1084 401.
E-mail address: beste@ifado.de (C. Beste).

0014-4886/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.expneurol.2008.11.018

potential (LRP) reflects the time course of unilateral movement execution (Praamstra et al., 1996; Coles et al., 1988). As the LRP only reflects the difference of activation between the contralateral and the ipsilateral hemisphere we additionally examine contra- and ipsilateral hemisphere independently of each other (Taniguchi et al., 2001; Yordanova et al., 2004; Carbonell et al., 2004). Negativities above the contralateral hemisphere reflect cortical activation during the response, positivities above the ipsilateral hemisphere reflect the inhibition of the alternate effector (i.e. response hand) (Taniguchi et al., 2001; Yordanova et al., 2004).

Based on the above mentioned neuronal alterations in HD affecting inhibitory basal ganglia systems (i.e. dysfunctions of MSNs, left lateralization of striatal damage), we hypothesize that symptomatic HDs may reveal altered inhibitory MRPs, but also increased excitatory MRPs predominantly for the right hand. The left hand may be less affected. Examining the precise time course of contra and ipsilateral processes during movement execution and possible lateralized deficits in un-medicated HD patients goes beyond existing studies on neurophysiological processes in movement execution in HD (Johnson et al., 2002, 2001; Berardelli et al., 1999).

However, recent studies indicate that neuronal processes in the motor system are preceded by neuronal processes occurring in parietal areas (Jaffard et al., 2008). These parietal processes may be well reflected by the parietal P3, which may also be related to above mentioned inhibitory potentials generated by motor cortices (Roman et al., 2005; Verleger et al., 2005). The P3 has been related to the reset or closure of cognitive processes (Verleger, 1988) and to inhibitory processes in general (Roberts et al. 1994). Hence we also explore possible changes in these processes, as reflected in the P3. If these are also altered, this may suggest for a cognitive contribution to deficits in voluntary movement execution in HD.

Materials and methods

Participants

In total, twenty-one HD subjects participated in the study. Of these, nine were right-handed, unmedicated patients (N=9) from 26 to 57 years of age (M=38.22; SD=9.14) with manifest symptoms (HD). Besides these, a group of twelve right-handed presymptomatic gene mutation carriers (N=12) defined by a positive gene tests and the absence of specific motor symptoms (pHD) from 24 to 56 years of age (M=35.91; SD=9.30) were recruited. Test scores and parameters of clinical relevance (e.g. CAG-repeat, UHDRS, TFC, BDI, YMRS) as well as neuropsychological testing are given in Table 1. All patients and pHDs agreed to be videotaped to document their neurological status. Neurological assessment of the pHD group revealed no symptoms specific for HD.

Besides these HD groups, a group of eleven right-handed, healthy controls was recruited. Detailed demographic data is given in Table 1, too. The experiments were undertaken with the understanding and written consent of each subject, with the approval of the appropriate local ethics committee, and in compliance with national legislation and the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki). The study was approved by the ethics committee of the University of Bochum.

Stimuli and procedures

Movement-related brain potentials were measured in a very easy choice reaction task (CRT) to minimise cognitive load and focus on speeded response activation. In this task an arrowhead was presented pointing either to the left or right. The subjects had to respond with the thumbs, each pressing a key depending on the direction of the arrowhead. Two blocks of 60 stimuli each were presented in this task randomly directing to the left and right, balanced across the left and right hand. The stimuli (1.5×1.5 cm) were presented for 100 ms. The response–stimulus interval (RSI) was set at a mean of 1000 ms with a random jitter of 200 ms, i.e. RSI was from 800 till 1200 ms. The upper bound of reaction time (RT) was set at 1100 ms, the lower bound at 100 ms. If a reaction fell outside this interval, the reaction was classified as erroneous.

Table 1
Descriptive analysis of ages, sex, handedness (LQ) as well as clinical data including cognitive and psychiatric assessment of all groups

	HD mean (SD)	pHD mean (SD)	Controls mean (SD)
Sample size	N=9	N=11	N=11
Male:female	5 m:4 f	6 m:5 f	6 m:5 f
Laterality quotient (LQ)	94.44 (5.27)	95.00 (4.82)	94.54 (5.22)
Age (years)	38.22 (9.14)	35.91 (10.03)	37.50 (8.35)
CAG-repeat size	46.11 (4.70)	42.58 (1.78)	NA
Age of onset (AO)	36.11 (10.39)	NA	NA
Estimated age of onset (eAO)	39.24 (10.21)	46.04 (4.89)	NA
Duration until eAO	−0.12 (8.62)	10.13 (8.19)	NA
UHDRS (motor score)	25.44 (9.03)	0	NA
TFC	12	13	NA
IS	87.22 (9.05)	100	NA
IQ	105.88 (8.10)	109.50 (11.86)	114.30 (5.86)
UHDRS (cognitive score)	187.55 (69.48)	236.50 (16.81)	249.50 (0.53)
MMSE	27.77 (2.33)	29.25 (0.86)	29.66 (0.49)
BDI	5.44 (4.03)	6.83 (6.61)	3.00 (3.08)
YMRS	5.33 (5.31)	1.33 (1.37)	1.45 (1.34)

The LQ is calculated as $[(R-L)]/(R+L)]\times 100$, resulting in values between −100 and +100. Positive values indicate dextrality, negative values indicate sinistrality. Abbrevations: UHDRS = Unified Huntington's disease Rating Scale, TFC = Total Functional Capacity Scale, IS = Instrumental Scale, MMSE = Mini Mental Status Examination, BDI = Beck Depression Inventory, YMRS = Young Mania Rating Scale. Note: No standard deviations (SD) are given for the TFC score, as the score was identical for all subjects within each group.

EEG data acquisition and pre-processing

During the task the EEG was recorded from 32 electrodes (Ag/AgCl) (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, FC5, FC6, Cz, C3, C4, C7, C8, Pz, P3, P4, P7, P8, Oz, O1, O2, M1, M2), two lateral and four vertical EOG electrodes at a sampling rate of 500 Hz. This was done using a QuickAmp (Brain Procducts Inc., Munich). The EEG was recorded by means of the Brain Vision Recorder sofware (Brain Products Inc., Munich).

Impedances were kept below 5 kΩ. Cz was used as primary reference. The filter bandwidth was from DC to 80 Hz. The EEG was analysed off-line using the Brain Vision Analyser sofware (Brain Products Inc., Munich).

Here, the EEG was digitally filtered off-line using a 0.10 Hz high-pass and 20 Hz low-pass filter. From the EEG response-locked ERPs were computed for each hand separately, beginning −600 ms before and ending 900 ms after the correct response followed by a baseline correction −600 ms to −400 ms. After this, eye movement artifacts were corrected with the Gratton–Coles-Algorithm using the EOG data (Gratton et al., 1983). Remaining artifacts were rejected using an amplitude criterion of ±80 μV. Before LRP calculation, the current source density (CSD) of the signals was calculated (Nunez et al., 1997). This eliminates the reference potential (see: Yordanova et al., 2004; Carbonnell et al., 2004). LRPs and activity on either the contralateral and ipsilateral hemisphere (MRPs) (Taniguchi et al., 2001) were calculated for each hand separately. Activity was measured using the electrodes C3 and C4 overlying the hand area of the motor cortex (Seiss and Praamstra, 2004; Carbonnell et al., 2004). Because of the low signal-to-noise ratio of LRPs a jack-knifing-procedure was applied before data quantification (Ulrich and Miller, 2001). To obtain the jackknifed mean LRPs onset score or amplitude j_i for each participant i (i=1…n), first, n grand-average wave forms are calculated across

participants by successively omitting every participant once. Then, for each of the *n* grand-average wave forms, the LRP onset or amplitude is measured. This results in *n* jackknifed LRP onset or amplitude scores ($j…j_n$), with each j_i being based on the data from all participants but *i* (see: Stahl and Gibbons, 2004). The idea behind jack-knifing is to reduce noise before LRP-onset or -peak detection is made with the effect of a more reliable onset-latency and peak-amplitude measurement. As jack-knifing leads to a massive reduction of variance in the electrophysiological data, these *F*-values were adjusted using the method described by Ulrich and Miller (2001) and denoted as Fcorr in the Results section.

Data analyses: ERPs

For the statistical analysis, behavioural data (reaction time (RT) and error rate) and electrophysiological measures (onset latency, peak-amplitude and peak-amplitude latency) were obtained. The onset latency was defined by that point of time in which the deviation from baseline reached a value of 20% of total peak to baseline amplitude (20%-criterion) (see also: Beste et al., 2007a). Amplitudes of the ERPs were evaluated relative to baseline. The LRP and the ipsi- and contralateral activity were analysed separately. Analyses of variance (ANOVAs) were conducted for LRPs and MRPs, including hand and group information. The LRP-peak and contralateral MRP-peak was defined as the most negative deflection before reaction at C3 and C4. The ipsilateral MRP-peak was defined as the first most positive peak after response execution at electrodes C3 and C4. The response-locked P3 was measured at electrode Pz and defined as the first positive peak after the response.

Results

Behavioural data

To assess group differences, RTs were subjected to a repeated measures ANOVA with hand (left vs. right) as within-subject factor and group (control, pHD and HD) as between-subject factor. RT means and SEM are given in Table 2.

There was a main effect of Group ($F(2,29)=19.23$; $p<0.001$). Bonferroni-corrected post-hoc tests revealed that the RTs were significantly slower in HD than in pHD and controls. The pHD- and control group did not differ from each other ($p>0.9$), but each of these differed from the HD-group (pHD: $p<0.018$ and controls: $p<0.010$, respectively). Further, there was a significant main effect of Hand ($F(1,29)=133.03$; $p<0.001$) with RTs being longer for the left (408.3±5.3 ms) than for the right hand (378.5±5.7 ms). Moreover, the interaction between group and hand was significant ($F(2,29)=39.12$; $p<0.001$). Analysing RT-differences between the hands within each group, it is shown that the control group demonstrated differences between the left and right hand ($F(1,10)=162.33$; $p<0.001$). The same was found for the HD-group ($F(1,8)=55.33$; $p<0.001$). In the pHD-group, no difference was seen between the hands ($F(1,11)=1.71$; $p=0.217$).

Lateralized readiness potentials (LRP)

The LRPs of the left and right hand for each group are illustrated in Fig. 1 (blue curves).

Peak amplitudes of the LRP were analysed with a repeated-measures ANOVA, using "hand" as within-subject factor and "group" as between-subject factor. LRP peak amplitudes were smaller for the left hand (−16.69±0.10 μV/m^2) compared to the right hand (−28.37±0.09 μV/m^2) (Fcorr(1,29)=6.96; $p=0.013$). All other main effects or interactions did not approach significance (all Fcorr's<0.11; $p>0.8$). For the peak latencies and for the onset latencies no main effect or interaction was significant (all Fcorr's<0.24; $p>0.6$). As can be seen, the LRP yields strong differences after the response. These will be analysed in the MRPs below.

Table 2
This table denotes mean RTs (ms) separated for the left and right hand, as well as both hands for each group

	HD mean (SEM)	pHD mean (SEM)	Controls mean (SEM)
Left hand (RT)	475.1 (11.0)	376.0 (8.0)	373.9 (9.1)
Right hand (RT)	414.9 (12.5)	372.5 (9.0)	348.1 (7.7)
Both hands (RT)	445.1 (10.3)	374.2 (8.9)	365.4 (9.3)

Dispersion parameters were determined with the jackknifed data.

Movement-related potentials (MRPs)

Fig. 1 also shows the contralateral and ipsilateral movement-related potentials (MRPs) for both hands. Before the response both MRPs appear unsuspicious. However, after the response the MRPs differed dramatically between groups, since after the response the symptomatic group showed a renewed massive activation of the contralateral and, shortly thereafter, of the ipsilateral hemisphere. This was restricted to right hand movements.

Contralateral hemisphere

Contralateral MRPs prior response were analysed in a repeated-measures ANOVA with "hand" as within-subject factor and "group" as between-subject factor. The contralateral MRP amplitudes did not differ between the hands (Fcorr(1,29)=0.47; $p=0.495$) and groups (Fcorr(2,29)=0.06; $p=0.942$). There was also no interaction of group and hand (Fcorr(2,29)=0.04; $p>0.9$). The same is found when analysing peak-latencies (*Fs* corr<0.55; $p>0.4$) and onset-latencies (*Fs* corr<0.10; $p>0.9$). However, as can be seen in Fig. 1, the symptomatic group showed another burst of activation above the contralateral hemisphere after the response, but only for the right hand. This "post-response potential" will be analysed separately, as outlined below.

Ipsilateral hemisphere (amplitudes)

Ipsilateral potentials, which are maximal after the response, were also analysed in a repeated-measures ANOVA with "hand" as within-subject factor and "group" as between subject factor. Means and SEM of the amplitudes as well as of the amplitude latencies are given in Table 3.

For the peak amplitudes, the ANOVA revealed no differences between the hands (Fcorr(1,29)=0.98; $p=0.330$). Yet, there was a significant interaction with the factor group (Fcorr(2,29)=5.29; $p=0.011$). Univariate ANOVAs revealed significant group differences for the right hand (Fcorr(2,29)=40.02; $p<0.001$), but not for the left hand (Fcorr(2,29)=0.35; $p=0.706$). Bonferroni-corrected post-hoc tests for the right hand revealed that the pHD- and control group had positive amplitudes, differing from each other ($p<0.001$). The symptomatic group did not show a positive but a negative amplitude ($p<0.001$).

Comparing the hands within each group it is revealed that the control group showed similar amplitudes between the hands (Fcorr(1,10)=3.17; $p=0.105$). For the pHD-group, differences in amplitudes were found between hands (Fcorr(1,11)=10.15; $p=0.009$). The same was found for the HD-group (Fcorr(1,8)=168.45; $p<0.001$) (see Table 3).

Ipsilateral hemisphere (latencies)

The peak latencies differed between the hands (Fcorr(1,29)=13.50; $p=0.001$) and this effect was further modulated by the factor group as the interaction reveals (Fcorr(2,29)=4.91; $p=0.015$). Subsequent

univariate ANOVAs revealed a significant main effect of group for the left hand (Fcorr(2,29)=10.90; $p<0.001$). Post-hoc tests revealed that the peak latencies for the HD and control group did not differ from each other ($p=0.767$). The pHD-group showed a much shorter latency than HDs ($p<0.001$) and controls ($p<0.001$). For the right hand, the univariate ANOVA also showed a significant main effect of Group (Fcorr(2,29)=7.27; $p=0.003$). Bonferroni-corrected post-hoc tests revealed that the HD- and pHD-group did not differ from each other ($p=0.175$). The control group revealed a longer latency than HD and pHD ($p<0.001$). Comparing hand differences within each group, it is shown that the control group demonstrated strong differences between the left and right hand (Fcorr(1,10)=17.08; $p=0.002$). Also the HD-group showed strong differences between the left and right hand (Fcorr(1,8)=463.59; $p<0.001$). Contrary, the pHD-group did not show differences (Fcorr(1,11)=0.20; $p=0.658$). As can be seen in Fig. 1, the HD-group revealed a negative peak deflection over the ipsilateral hemisphere after the response, slightly after the negativity above the contralateral hemisphere. This ipsilateral negativity was only seen for right-hand responses.

MRPs and P3

Fig. 2 shows the MRPs over the contra and ipsilateral hemisphere (at electrodes C3 and C4) in relation to the P3 at electrode Pz. The amplitudes and latencies of potentials at Pz and the ipsilateral MRPs at C3 and C4 (for left and right hand usage respectively) were analysed in a repeated measures ANOVA. Electrode (Pz, C3, C4) and hand were within-subject factors. Group was the between subject factor.

There was a main effect of hand (Fcorr(1,29)=4.16; $p=0.050$). Amplitudes were larger for the left (37.7±0.16) than for the right hand (23.1±0.2). There was also a main effect of group (Fcorr(2,29)=30.94; $p<0.001$). The HD-group showed negative amplitudes (−21.3±0.27), while the controls (51.2±0.24) and pHDs (61.4±0.23) had positive amplitudes not differing from each other ($p=0.143$). Further there was an interaction "hand×group" (Fcorr(2,29)=16.63; $p<0.001$). Group differences were mainly due to the right hand responses. The HD-group showed negative amplitudes, whereas the control and pHD-group showed positive ones. For left hand responses amplitudes were positive in all groups. All other effects did not reach level of significance (all Fs<1.44; $p>0.2$).

The latencies differed between the hands (Fcorr(1,29)=33.50; $p<0.001$), being longer for the left (128.7 ms±0.16) than for the right hand (102.4 ms±0.12). This effect was further modulated by the factor group as the interaction reveals (Fcorr(2,29)=17.05; $p<0.001$). It is shown that latencies for the left and right hand differed from each other in the HD-group (left: 155.4 ms±0.41; right: 94.1 ms±0.17) and controls (left: 169.8 ms±0.21; right: 147.8 ms±0.15), but not in the pHD-group (left: 60.8 ms±0.84; right: 65.5 ms±0.85). The main effect group was significant, too (Fcorr(2,58)=56.01; $p<0.001$). Here, the controls showed the longest latencies (158.8 ms±0.21), followed by the HD- (124.7 ms±0.23) and pHD-group (63.2±0.20). All groups differed from each other ($p<0.001$). Finally there was a main effect of electrode (Fcorr(2,58)=12.20; $p<0.001$). Here, latencies were shortest at electrode Pz (90.7 ms±0.18), followed by the contralateral (132 ms±0.16) and ipsilateral electrode (124.1 ms±0.26). All other effects were not significant (all Fs<1.23; $p>0.3$).

Post-response potentials (contralateral hemispheres)

As already mentioned, negative post-response MRPs were seen above the contralateral hemisphere exclusively in the HD-group after right hand movements. These post-response peaks were defined as the most negative peak on the contra- and ipsilateral hemisphere after the response. The post-response excitation above the contralateral hemisphere (−43.61±0.15 μV/m^2) was stronger than the normal contralateral pre-response MRP (−11.56±2.77 μV/m^2) (Fcorr(1,8)=162.3; $p<0.001$).

Table 3
This table presents mean amplitudes (μV/m^2) as well as mean latencies (ms) for of the potential above the ipsilateral hemisphere for the left and right hand, separated for each group

Ipsilateral	HD mean (SEM)	pHD mean (SEM)	Controls mean (SEM)
Left hand (amplitude)	20.63 (0.66)	39.47 (0.74)	45.13 (0.5)
Right hand (amplitude)	−38.84 (0.40)	65.97 (0.09)	46.0 (0.2)
Left hand (amplitude latency)	173.4 (0.4)	72.5 (0.5)	181.9 (0.7)
Right hand (amplitude latency)	96.8 (0.3)	74.1 (0.6)	145.7 (0.1)

Pearson-correlation revealed that the strength of the MRP and the post-response potential was related ($r=0.723$; $R^2=0.51$; $p=0.014$).

Besides this negative contralateral post-response potential, the peak over the ipsilateral (right) hemisphere (normally positive) was also negative in the HD group. The ipsilateral potential (−32.08±0.22 μV/m^2) was smaller than the contralateral post-response potential (−43.61±0.15 μV/m^2) (Fcorr(1,8)=14.23; $p=0.005$). The amplitudes of the ipsilateral potential and the contralateral potential were highly correlated ($r=0.886$; $R^2=0.77$ $p=0.001$). The contralateral MRP peaked earlier (109.3±0.5 ms) than the ipsilateral MRP (151.1±0.4 ms) (Fcorr(1,8)=55.21; $p<0.001$). If these post-response activities (PRA) were due to such involuntary choreatic movements, one would expect them to correlate with the UHDRS motor score assessing such symptoms, which was not the case (contralateral PRA: $r=0.370$; $p=0.163$; ipsilateral PRA: $r=-0.039$; $p=0.460$). Also when the hyperkinesia subscore (specifically measuring chorea) was used separately no correlation was found (contralateral PRA: $r=0.120$; $p=0.379$; ipsilateral PRA: $r=-0.156$; $p=0.344$).

Discussion

This study investigated voluntary movement execution in different stages of Huntington's disease (pHD and HD) and healthy controls.

The behavioural data revealed an increase in reaction times (RTs) in the HD-group. While the control group showed faster RTs with the dominant right hand compared to the left hand, the pHD-group showed a symmetric pattern (i.e. no difference between the hands). In the HD-group, the difference in RTs between the dominant and the non-dominant hand was higher compared to controls. Parameters of excitatory MRPs preceding the response did not differ between the groups. The pHD-group showed an increased inhibition above the ipsilateral hemisphere for right hand movements. Furthermore, ipsilateral peak latencies paralleled the lack of difference in RTs between the hands. In contrast to the pHDs, the symptomatic HD group did not show inhibition and rather a second excitation above the contralateral hemisphere. Shortly thereafter a similar activation above the ipsilateral hemisphere occurred. This effect was restricted to right hand movements. These post-response activities are not likely to be due to an artifact (e.g. involuntary movements), since the topographical maps showed that they are focused above the motor cortices. The study adds on existing literature regarding voluntary movement execution in HD examining processes of sequential motor movements in a tapping task (e.g. Johnson et al., 2001) focussing on premovement changes. Differences between these studies may due to methods and to the experimental procedure applied.

Contralateral hemisphere

Before movement execution, the pattern reflected in the "contralateral MRPs" is similar between all groups. This suggests that the neurophysiological processes occurring during voluntary response execution are similar for all groups. After the response, a second excitation is seen in the HD group, which was larger than the normal pre-response MRP. This extra excitation was limited to the dominant

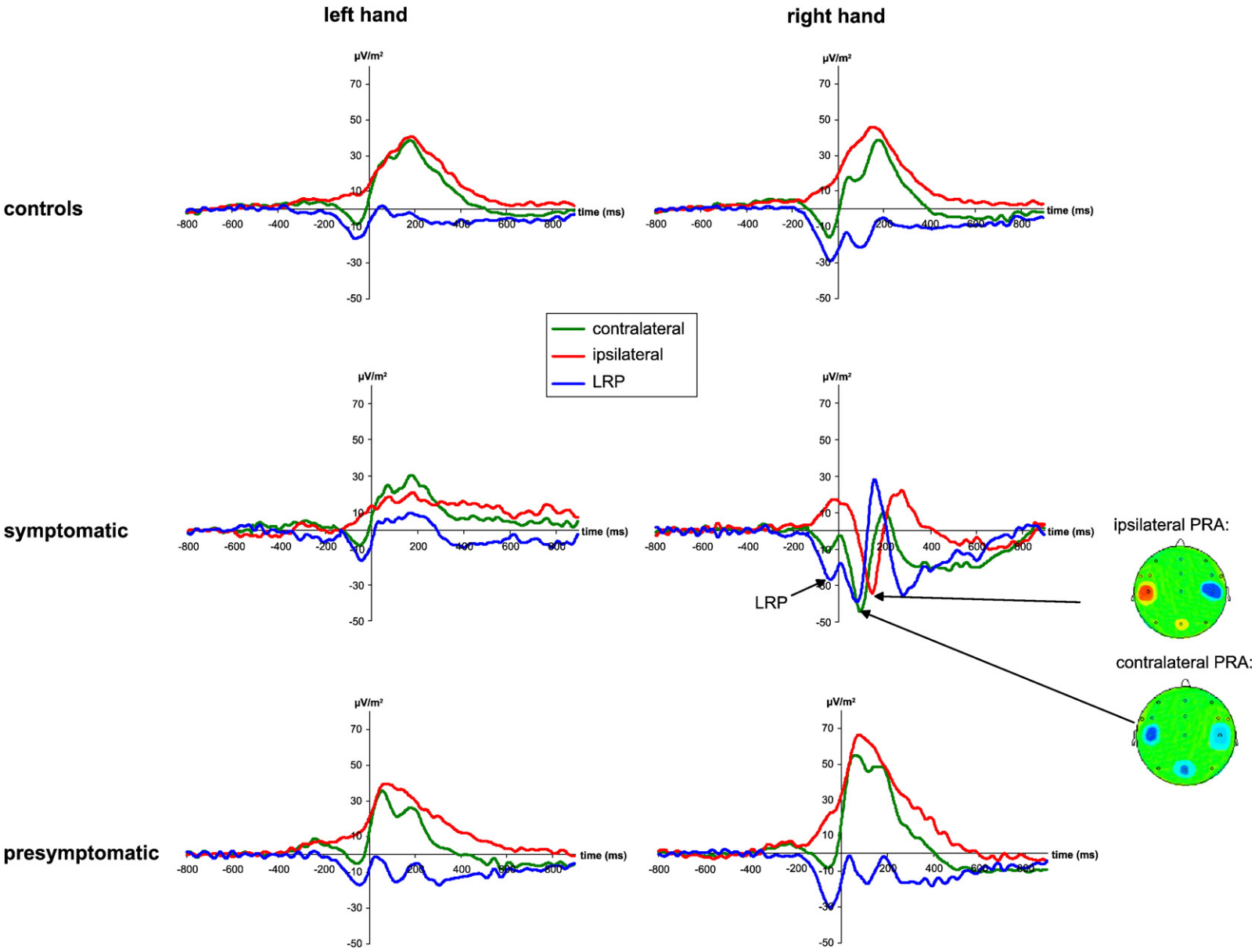

Fig. 1. The lateralized readiness potential (LRP) (blue line) as well as the MRP above the contralateral (green line) and the ipsilateral (red line) hemisphere. These are given, separated for left hand responses (left panel), right hand responses (right panel) and for the groups. Time 0 represents the moment of response execution.

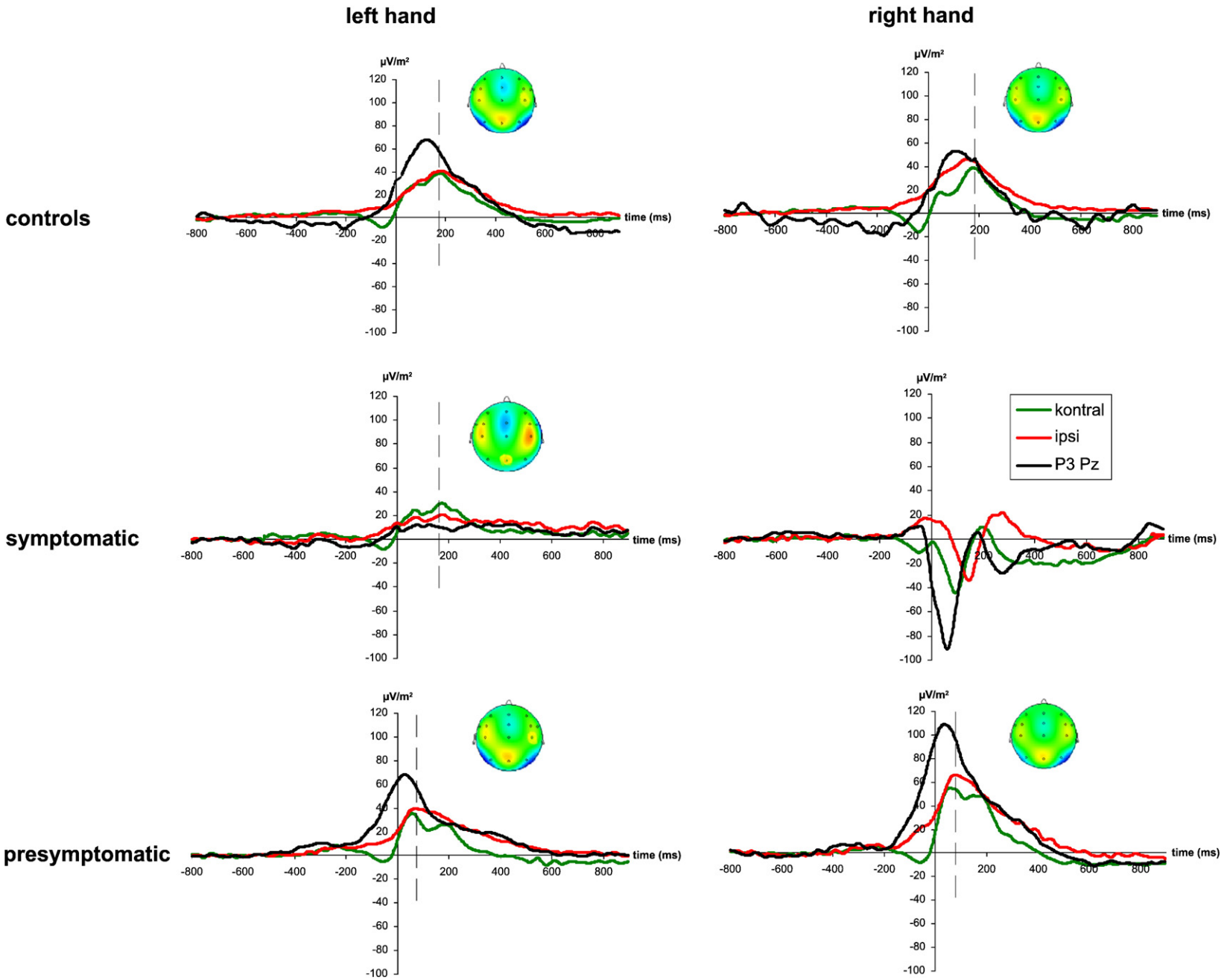

Fig. 2. The P3 at electrode Pz combined with the MRPs above the contralateral (green line) and ipsilateral (red line) hemisphere. These are given separated for left hand responses (left panel), right hand responses (right panel) and for the groups. Time 0 represents the moment of response execution. The Maps denote the time point of the maximum of positivity of the MRPs (at C3 and C4). As can be seen the P3 at electrode Pz peaks ealier than the MRPs and is cicrumscribed round this electrode.

left hemisphere (right hand). The excitation of the left cortical area was not fully inhibited before the post-response excitation. As structural neuroanatomical factors would be static and may not only influence the "post-response potentials", processes occurring between the pre-response and post-response MRPs may rely upon dynamic factors of changed neural transmission in HD (for review: Yohrling and Cha, 2002).

Cortical processes can recurrently influence thalamo-cortical processes (e.g. Emri et al., 2003; Blumenfeld and McCormick, 2000; Murer et al., 2002). It may be speculated that recurrent activity from the motor cortex after the initial response adds on residual activity, being evident in thalamo-cortical circuits. This entails increased excitatory post-response activity. Such a process is substantiated by the finding that the post-response excitation was related to the pre-response MRP. Inhibitory GABAergic neurotransmission is heavily altered in HD (Cepeda et al., 2007; Melone et al., 2005; Kendall et al., 2000). Consequently, the thalamic VA/VL complex (Purves, 2004; Gurney et al., 2004), connected to the primary motor cortex (M1) (e.g. Sommer, 2003), may be less inhibited in HD (Purves, 2004). Such a reduced inhibition of thalamic structures may putatively contribute to the post-response excitation. Thalamic structures may be more "vulnerable" to recurrent neuronal activity from cortical areas. Since GABAergic neurotransmission in HD is also affected in the motor cortex (Melone et al., 2005), a dysfunction of intracortical inhibitory circuits (e.g. McDonnell et al., 2006; Di Lazzaro et al., 2005; Chen, 2004) can also not be ruled out. The hypothetical processes are illustrated in Fig. 3.

Ipsilateral hemisphere

The usual positive MRP above the hemisphere ipsilateral to the effector is supposed to reflect inhibition of the alternative response. This may be mediated via transcallosal inhibition (Taniguchi et al., 2001). It has been shown that these processes are mediated by transcallosal fibres targeting GABAergic interneurons (e.g. Daskalakis et al., 2002; Ferbert et al., 1992; Hausmann et al., 2006). In the pHD-group, the inhibitory potential was stronger than in the control and symptomatic group, though the effect emerged exclusively for the dominant right hand. For the symptomatic group, the potential above the ipsilateral hemisphere turned negative approximately 42 ms after the post-response potential above the contralateral hemisphere. Again, this was only seen for the dominant right hand.

The finding in the pHD-group indicates that transcallosal inhibition and hence GABAergic neural transmission are increased in presymptomatic HD. In contrast, transcallosal inhibition and GABAergic neural transmission is dysfunctional in symptomatic HD (Melone et al., 2005) (see Fig. 4).

This increase in GABAergic neurotransmission in pHD might reflect a compensatory mechanism in the presymptomatic stage that are frequently observed in early stages of HD (e.g. Beste et al., 2007a, Feigin et al., 2006).

The activation of the ipsilateral hemisphere in the HD-group may originate from the contralateral hemisphere, because the amplitudes above the contra- and above the ipsilateral hemisphere were correlated. However, since the amplitude above the ipsilateral

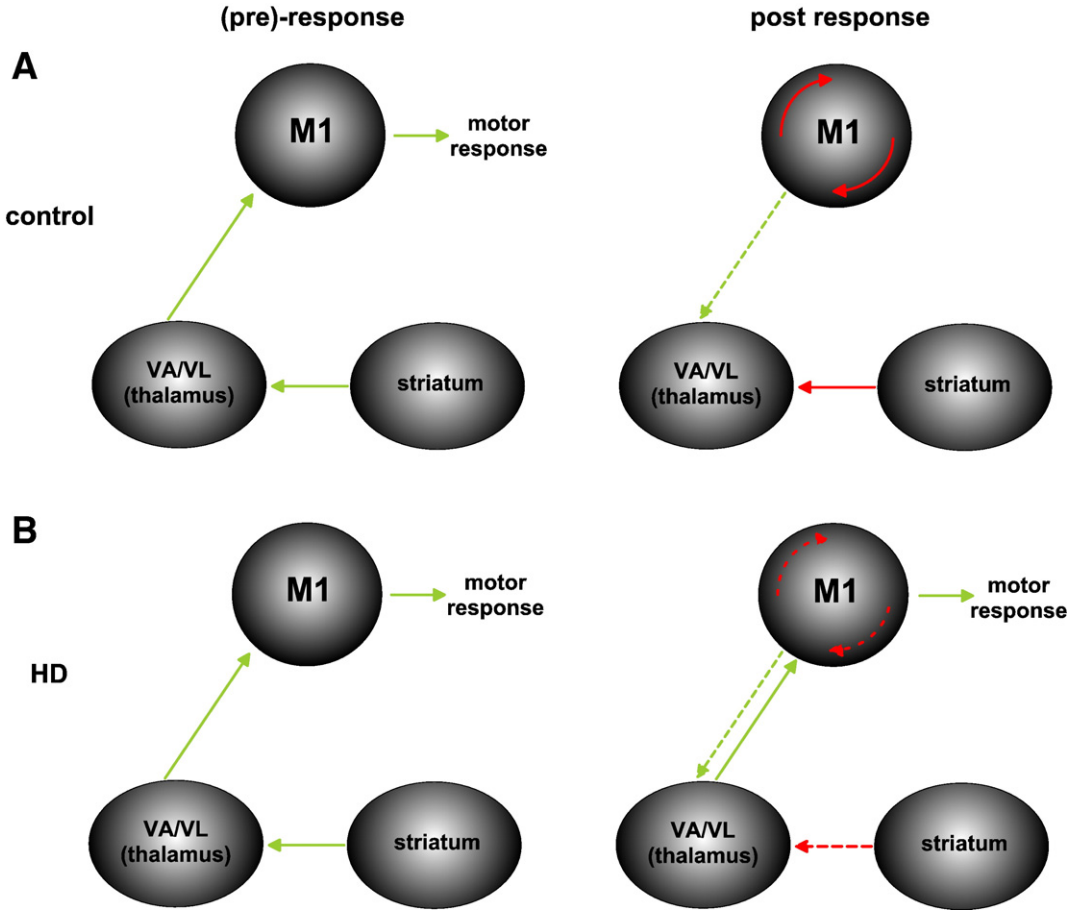

Fig. 3. Possible intrahemispheric processes. Green lines denote excitatory influence, red lines denote inhibitory influence. Processes occurring pre motor response are likely to be similar between controls (A) and HDs (B). In HDs (B) intracortical and striatal inhibitory processes are weakened. This may cause that the motor cascade is not terminated, which results in a second cortical activation and motor response. Note: circulated arrow-lines denote intracortical inhibitory processes. Dashed red lines denote dysfunctional inhibition processes. Dashed green lines denote recurrent excitatory activity.

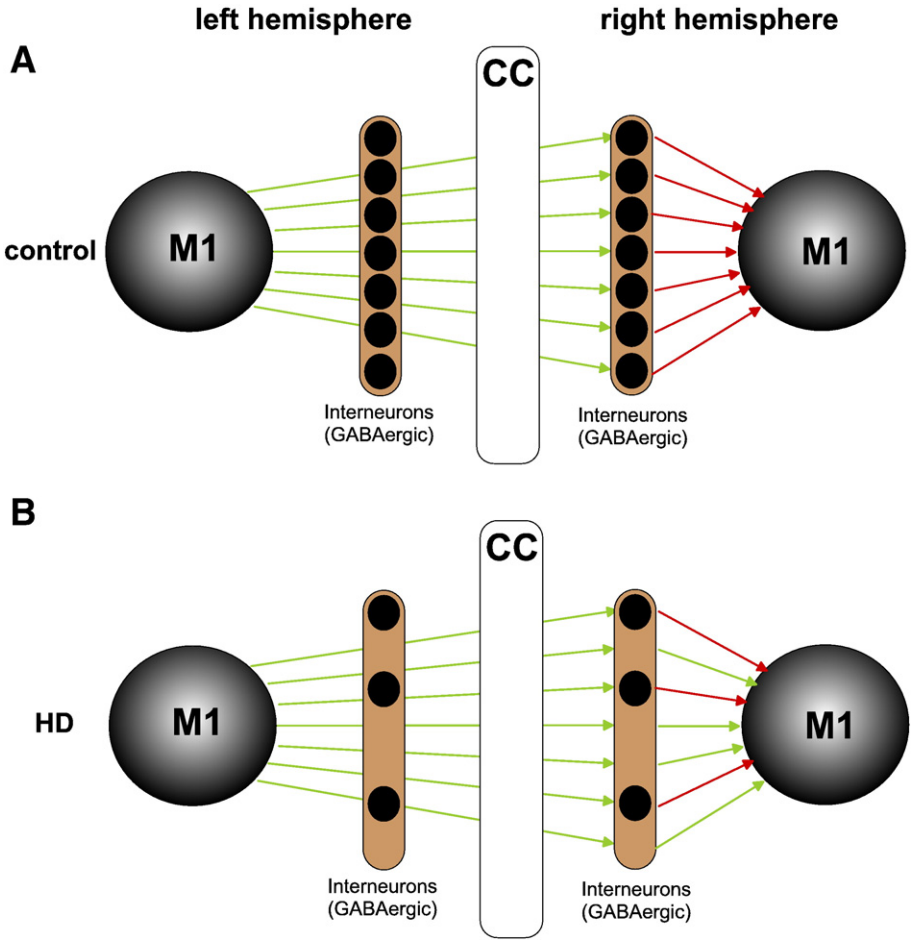

Fig. 4. Possible interhemispheric processes. Green lines denote excitatory influence, red lines denote inhibitory influence. (A) Left hemispheric activity from the primary motor cortex (M1) crosses the corpus callosum (CC) and activates GABAergic interneurons. These interneurons in turn entail an inhibition of the right primary motor cortex. (B) In HD GABAergic interneurons are lost. As a net result "activation" predominates over "inhibition" and the right motor cortex is activated. Note: Dashed red lines denote dysfunctional inhibition processes.

hemisphere was lower compared to the contralateral hemisphere, interhemispheric inhibition is not completely dysfunctional. Rather, processes mediating interhemispheric inhibition may only be able to suppress relatively low activation, but not stronger activations. This would also explain why no such pattern emerged after left hand movement (right hemisphere).

MRPs and parietal processes

In all groups both hemispheres were inhibited after the response, suggesting a total motor reset. Examining the relation of the post-response positivity to the (response-locked) parietal P3 (Falkenstein et al. 1994; Verleger et al. 2005) we showed that the P3 was larger and peaked earlier than the post-response positivity over the motor areas. A parietal involvement before motor inhibition has recently been reported (Jaffard et al., 2008) and interpreted as a command initiating and/or inhibiting a motor program (see also: De Jong et al., 2001). Such a pattern is also seen in our data.

In manifest HD this post-response inhibitory cascade is weakened in HD for left hand-responses and even inverted for right-hand responses. Hence in HD, the motor program is putatively not closed/inhibited, but activated again for right-hand responses. We tentatively suggest that alterations at the level of the motor cortex in HD are preceded by very similar alterations in parietal processing. Hence an alteration of cognitive processing appears to precede or possibly even induce the alteration of motor activation in HD (see also: Beste et al., 2007b). In Parkinson's disease it has alse been suggested that cognitive factors contribute to voluntary movement dysfunctions (Ballanger et al., 2007). Yet, it has to be noted that these influences were suggested to take place pre motor movement (premovement changes). The difference to the current results may be due to the different pathophysiologies of these diseases.

Motor dominance effects

The typical finding of faster RTs with the dominant (right) hand compared to the non-dominant (left) hand was strongly reduced in pHD. The pHD group revealed no difference between hands (see also Fig. 1), although right-handedness scores (Oldfield, 1971) were virtual identical between groups (see also Table 1).The reduced hand difference in RTs was paralleled by the peak-latencies of the inhibitory MRPs.

Early stages of neurodegenerative diseases have been characterized by compensatory processes (e.g. Beste et al., 2007a; Blum et al., 2003). The reduced hand-use difference in pHD can also be interpreted as compensatory. However, how can altered functional cerebral asymmetries compensate for functional (motor) deficits in pHDs? Compensatory mechanisms in pHD are mediated via adenosine receptors (e.g. Tarditi et al., 2006). As these receptors are co-expressed on striatal and cortical GABAergic neurons, they may also be important for motor functions (Ferre et al., 1993; Svenningsson et al., 1999). They may modulate striatal output function (e.g. Fisone et al., 2007; Gurney et al., 2004). GABAergic neurotransmission may be stimulated by increased activity of the adenosine receptor system leading to a symmetrical pattern of RTs (=reduced functional

asymmetries) and also the increased inhibition of the ipsilateral hemisphere in pHD. Future studies should integrate PET data to clarify the putative role of adenosine receptors.

Conclusions

In summary, the results suggest modulations of motor inhibition processes in HD, dependent on the stage of the disease. In pHD inhibition was found to be enhanced compared to normal controls, while in manifest HD a profound impairment of inhibition was found. Importantly, these modulations occur after the response and are restricted to the dominant motor system. Furthermore, the results indicate that preceding cognitive processes contribute to these motor dysfunctions. The dynamics observed in HD and pHD may be due to altered intra and interhemispheric processes. In future studies the usability of our ERP model for clinical studies examining drug effects should be explored.

Acknowledgments

This research was supported by a grant from FoRUM AZ- F479-2005, Ruhr-University Bochum. We thank all participants for their participation. We thank L. Blanke for committed technical assistance.

References

Aylward, E.H., Sparks, B.F., Field, K.M., Yallapragada, V., Shpritz, B.D., Rosenblatt, A., Brandt, J., Gourley, L.M., Liang, K., Zhou, H., Margolis, R.L., Ross, C.A., 2004. Onset and rate of striatal atrophy in preclinical Huntington's disease. Neurology 62, 66–72.

Ballanger, B., Gil, R., Audriffren, M., Desmurget, M., 2007. Perceptual factors contribute to akinesia in Parkinson's disease. Exp. Brain Res. 179, 245–253.

Beal, M.F., Ferrante, R.J., 2004. Experimental therapeutics in transgenic mouse models of Huntington's disease. Nat. Rev., Neurosci. 5, 373–384.

Berardelli, A., Noth, J., Thompson, P.D., Bollen, E.L., Curra, A., Deuschl, G., van Dijk, J.G., Töpper, R., Schwarz, M., Roos, R.A., 1999. Pathophysiology of chorea and bradykinesia in Huntington's disease. Mov. Disord. 14, 398–403.

Bevan, M.D., Magill, P.J., Teman, D., Bolam, J.P., Wilson, C.J., 2002. Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. Trends Neurosci. 25, 525–531.

Beste, C., Saft, C., Yordanova, J., Andrich, J., Gold, R., Falkenstein, M., Kolev, V., 2007a. unctional compensation or pathology in cortico-subcortical interactions in preclinical Huntington's disease. Neuropsychologia 45, 2922–2930.

Beste, C., Saft, C., Andrich, J., Müller, T., Gold, R., Falkenstein, M., 2007b. Time processing in Huntington's disease: a group-control study. PloS One 1 (1), e1263.

Beste, C., Saft, C., Konrad, C., Andrich, J., Habbel, A., Schepers, I., Jansen, A., Pfleiderer, B., Falkenstein, M., 2008. Levels of error processing in Huntington's disease: a combined study using event-related potentials and voxel-based morphometry. Hum. Brain Mapp. 29, 121–130.

Blum, D., Hourez, R., Galas, M.C., Popoli, P., Schiffmann, S.N., 2003. Adenosine receptors and Huntington's disease: implications for pathogenesis and therapeutics. Lancet Neurol. 2, 366–374.

Blumenfeld, H., McCormick, D.A., 2000. Corticothalamic inputs control the pattern of activity generated in thalamocortical networks. J. Neurosci. 20, 5153–5162.

Carbonell, L., Hasbroucq, T., Grapperon, J., Vidal, F., 2004. Response selection and motor areas: a behavioural and electrophysiological study. Clin. Neurophysiol. 115, 2164–2174.

Cepeda, C., Wu, N., Andre, V.M., Cummings, D.M., Levine, M.S., 2007. The corticostriatal pathway in Huntington's disease. Prog. Neurobiol. 81, 253–271.

Chen, R., 2004. Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp. Brain Res. 154, 1–10.

Coles, M.G., Gratton, G., Donchin, E., 1988. Detecting early communication: using measures of movement-related potentials to illuminate human information processing. Biol. Psychol. 26, 69–89.

Daskalakis, Z.J., Christensen, B.K., Fitzgerald, P.B., Roshan, L., Chen, R., 2002. The mechanisms of Interhemispheric inhibition in the human motor cortex. J. Physiol. 543, 317–326.

De Jong, B.M., van der Graaf, F.H., Paans, A.M., 2001. Brain activation related to the representations of external space and body scheme in visuomotor control. Neuroimage 14, 1128–1135.

Di Lazzaro, V., Pilato, F., Dileone, M., Tonali, P.A., Ziemann, U., 2005. Dissociated effects of diazepam and lorazepam on short-latency afferent inhibition. J. Physiol. 569, 315–323.

Emri, Z., Antal, K., Crunelli, V., 2003. The impact of corticothalamic feedback on the output dynamics of a thalamocortical neurone model: the role of synapse location and metabotropic glutamate receptors. Neuroscience 117, 229–239.

Feigin, A., Ghilardi, M.F., Huang, C., Ma, Y., Carbon, M., Guttman, M., Paulsen, J.S., Ghez, C.P., Eidelberg, D., 2006. Preclinical Huntington's disease: compensatory brain responses during learning. Ann. Neurol. 59, 53–59.

Falkenstein, M., Hohnsbein, J., Hoormann, J., 1994. Effects of choice complexity on different subcomponents of the late positive complex of the event-related potential. Electroencephalogr. Clin. Neurophysiol. 92, 148–160.

Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., Marsden, C.D., 1992. Interhemispheric inhibition of the human motor cortex. J. Physiol. 453, 525–546.

Ferre, S., O'Connor, W.T., Fuxe, K., Ungerstedt, U., 1993. The striopallidal neuron: a main locus for adenosine–dopamine interactions in the brain. J. Neurosci. 13, 5402–5406.

Finke, K., Bublak, P., Dose, M., Müller, H.J., Schneider, W.X., 2006. Parameter-based assessment of spatial and non-spatial attentional deficits in Huntington's disease. Brain 129, 1137–1151.

Fisone, G., Hakansson, K., Borgkvist, A., Santini, E., 2007. Signaling in the basal ganglia: postsynaptic and presynaptic mechanisms. Physiol. Behav. 92, 8–14.

Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. Electroencephalogr. Clin. Neurophysiol. 55, 468–484.

Gurney, K., Prescott, T.J., Wickens, J.R., Redgrave, P., 2004. Computational models of the basal ganglia: from robots to membranes. Trends Neurosci. 27, 453–459.

Hausmann, M., Tegenthoff, M., Sänger, J., Janssen, F., Güntürkün, O., Schwenkreis, P., 2006. Transcallosal inhibition across the menstrual cycle: a TMS study. Clin. Neurophysiol. 117, 26–32.

Jaffard, M., Longcamp, M., Velay, J.-L., Anton, J.-L., Roth, M., Nazarian, B., Boulinguez, 2008. Proactive inhibitory control of movement assessed by event-related fMRI. NeuroImage [Electronic publication ahead of print].

Johnson, K.A., Cunnington, R., Bradshaw, J.L., Chiu, E., Iansek, R., 2002. Effect of an attentional strategy on movement-related potentials recorded from subjects with Huntington's disease. Mov. Disord. 17, 998–1003.

Johnson, K.A., Cunnington, R., Iansek, R., Bradshaw, J.L., Geargiou, N., Chiu, E., 2001. Movement-related potentials in Huntington's disease: movement preparation and execution. Exp. Brain Res. 138, 492–499.

Kassubek, J., Juengling, F.D., Ecker, D., Landwehrmeyer, G.B., 2005. Thalamic atrophy in Huntington's disease co-varies with cognitive performance: a morphometric MRI analysis. Cereb. Cortex 15, 846–853.

Kendall, A.L., Hantraye, P., Palfi, S., 2000. Striatal tissue transplantation in non-human primates. Prog. Brain Res. 127, 381–404.

Kremer, B., 2002. Clinical neurology of Huntington's disease. In: Bates, G., Harper, P., Jones, L. (Eds.), Huntington's disease. Oxford University Press, Oxford, pp. 28–61.

McDonnell, M.N., Orekhov, Y., Ziemann, U., 2006. The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. Exp. Brain Res. 173, 86–93.

Melone, M.A., Jori, F.P., Peluso, G., 2005. Huntington's disease: new frontiers for molecular and cell therapy. Curr. Drug Targets 6, 43–56.

Murer, M.G., Tseng, K.Y., Kasanetz, F., Belluscio, M., Riquelme, L.A., 2002. Brain oscillations, medium spiny neurons, and dopamine. Cell. Mol. Neurobiol. 22, 611–632.

Nunez, P.L., Srinivasan, R., Westdorp, A.F., Wijesinghe, R.S., Tucker, D.M., Silberstein, R.B., 1997. EEG coherency. I: statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. Electroencephalogr. Clin. Neurophysiol. 103, 499–515.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Penney, J.B., Young, A.B., Shoulson, I., Starosta-Rubenstein, S., Snodgrass, S.R., Sanchez-Ramos, M., Ramos-Arroyo, M., Gomez, F., Penchaszadeh, G., Alvir, J., 1990. Huntington's disease in Venezuela: 7 years of follow-up on symptomatic and asymptomatic individuals. Mov. Disord. 5, 93–99.

Praamstra, P., Meyer, A.S., Cools, A.R., Horstink, M.W., Stegeman, D.F., 1996. Movement preparation in Parkinson's disease. Time course and distribution of movement-related potentials in a movement precueing task. Brain 119, 1689–1704.

Purves, D., 2004. Modulation of Movement in the basal ganglia, In: Purves, D., Augustine, G.J., Fitzpatrick, D., Hall, W.C., LaMantia, A.-S., McNamara, J.O., Williams, S.M. (Eds.), Neuroscience, 3rd edition. Sinauer Associates, Sunderland. Chapter 18.

Roberts, L.E., Rau, H., Lutzenberger, W., Birbaumer, N., 1994. Mapping P300 waves onto inhibition: Go/Nogo discrimination. Electroencephalogr. Clin. Neurophysiol. 92, 44–55.

Roman, R., Brazdil, M., Jurak, P., Rektor, I., Kukleta, M., 2005. Intracerebral P3-like waveforms and the length of the stimulus–response interval in a visual oddball paradigm. Clin. Neurophysiol. 116, 160–171.

Rosas, H.D., Feigin, A.S., Hersch, S.M., 2004. Using advances in neuroimaging to detect, understand, and monitor disease progression in Huntington's disease. NeuroRx 1, 263–272.

Seiss, E., Praamstra, P., 2004. The basal ganglia and inhibitory mechanisms in response selection: evidence from subliminal priming of motor responses in Parkinson's disease. Brain 127, 330–339.

Sommer, M.A., 2003. The role of the thalamus in motor control. Curr. Opin. Neurobiol. 13, 663–670.

Stahl, J., Gibbons, H., 2004. The application of jackknife-based onset detection of lateralized readiness potential in correlative approaches. Psychophysiology 41, 845–860.

Svenningsson, P., Le Moine, C., Fisone, G., Fredholm, B.B., 1999. Distribution, biochemistry and function of striatal adenosine A2A receptors. Prog. Neurobiol. 59, 355–396.

Taniguchi, Y., Burle, B., Vidal, F., Bonnet, M., 2001. Deficit motor cortical activity for simultaneous bimanual responses. Exp. Brain Res. 137, 259–268.

Tarditi, A., Camuri, A., Varani, K., Borea, P.A., Woodman, B., Bates, G., Cattaneo, E., Abbracchio, M.P., 2006. Early and transient alteration of adenosine A2A receptor signalling in a mouse model of Huntington's disease. Neurobiol. Dis. 23, 44–53.

Thieben, M.J., Dugins, A.J., Good, C.D., Gomes, L., Mahant, N., Richards, F., McCusker, E., Frackowiak, R.S., 2002. The distribution of structural neuropathology in pre-clinical Huntington's disease. Brain 125, 1815–1828.

Ulrich, R., Miller, J., 2001. Using the jackknife-based scoring method for measuring LRP onset effects in factorial designs. Psychophysiology 38, 816–827.
Van Vugt, J.P., van Hilten, B.J., Roos, R.A., 1996. Hypokinesia in Huntington's disease. Mov. Disord. 11, 384–388.
Van Vugt, J.P., Piet, K.K., Vink, L.J., Siesling, S., Zwinderman, A.H., Middelkoop, H.A., Roos, R.A., 2004. Objective assessment of motor slowness in Huntington's disease: clinical correlates and 2-year follow-up. Mov. Disord. 19, 285–297.
Verleger, R., 1988. Event-related potentials and cognition: a critique of the context updating hypothesis and an alternative interpretation of P3. Behav. Brain. Sci. 11, 343–356.
Verleger, R., Jaskowski, P., Wascher, E., 2005. Evidence for an Integrative role of P3b in linking reaction to perception. J. Psychophysiol. 19, 165–181.
Wickens, J.R., Wilson, C.J., 1998. Regulation of action-potential firing in spiny neurons of the rat neostriatum in vivo. J. Neurophysiol. 79, 2358–2364.
Yohrling, G.J., Cha, J.H., 2002. Neurochemistry of Huntington's disease. In: Bates, G., Harper, P., Jones, L. (Eds.), Huntington's disease. Oxford University Press, Oxford, pp. 276–308.
Yordanova, J., Kolev, V., Hohnsbein, J., Falkenstein, M., 2004. Sensorimotor slowing with ageing is mediated by a functional dysregulation of motor-generation processes: evidence from high-resolution event-related potentials. Brain 127, 351–362.