Levels of Error Processing in Huntington's Disease: A Combined Study Using Event-Related Potentials and Voxel-Based Morphometry

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Abstract: Huntington's Disease (HD) is a neurogenetic disorder accompanied by an atrophy of the striatum and hence of the dopaminergic (DA) system. Neural processes subserving error processing presumably depend on the DA system. We assessed error processing in manifest HD and in presymptomatic HD-gene-mutation-carriers (pHD) with event-related potentials reflecting error processing (the error negativity or error-related negativity and the error positivity derived from a flanker-task). We found a reduction of the Ne in the case of HD compared to pHD reflecting dopamine system pathology. Despite the Ne being reduced in HD, behavioral adaptation was possible. In addition, the error-rates did not differ between the groups. Optimized voxel-based morphometry revealed that grey matter volume in the medial frontal gyrus is correlated with the Ne amplitude in symptomatic patients. In addition, the effect of a Ne-reduction was related to the grey matter underneath the medial frontal gyrus, which is in line with two theories of the Ne. In contrast, the Pe did not differ between the groups, suggesting that the Pe is decoupled from the DA system. Interestingly we found a reduction of a late slow negativity on correct responses, which possibly reflects decreased preparatory processes in HD compared to pHD as induced by the DA alterations in HD. In conclusion a deterioration in error processing in HD compared to pHD is mainly reflected by the Ne. The deterioration might rely on two factors: a neurofunctional and a neuroanatomical. *Hum Brain Mapp* 29:121–130, 2008. ©2007 Wiley-Liss, Inc.

Key words: Huntington's disease; neurodegeneration; event-related potentials (ERP); error processing; voxel-based morphometry (VBM); MRI

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INTRODUCTION

Huntington's disease (HD) is an autosomal dominant disorder accompanied by a degeneration of the neostriatum [Heinsen et al., 1994]. HD is accompanied by a reduction in D1 and D2 receptor density [Ginovart et al., 1997] in manifest [Turjanski et al., 1995] as well as in the preclinical state [Augood et al., 1997; Backman et al., 1997]. Other transmitter systems are altered, too [Yohrling and Cha, 2002]. Neuroanatomical pathology is also seen in both stages of disease [Thieben et al., 2002] and not limited to the striatum [for review see: Gutekunst et al., 2002]. HD and pHD are accompanied by a decline in various cognitive functions [Lawrence et al., 1998], such as a deficit in error-feedback control [Smith et al., 2000], which might be one reason for the prominent motor symptoms.

Error processing is a basic cognitive function, which induces corrective and adaptive actions [Yordanova et al., 2004], such as error correction and a slowing of the response after an error [Debener et al., 2005; Rabbitt, 1966]. Error processing is reflected in the event-related potential (ERP) after an incorrect response as a negative component, the error (related) negativity [Ne or error-related negativity (ERN); Falkenstein et al., 1990; Gehring et al., 1993] and the subsequent error positivity (Pe) [Falkenstein et al., 1990, 1991], which are thought to reflect early error detection and late conscious error recognition, respectively [Falkenstein et al., 1990, 2000; Leuthold and Sommer, 1999; Overbeek et al., 2005]. A prominent recent theory of the Ne proposes that the midbrain dopaminergic (DA) system and the anterior cingulate cortex (ACC) interact in producing the Ne. If an event is worse than expected (i.e. an error), the DA system sends a signal to the ACC, which in turn elicits the Ne [Holroyd and Coles, 2002; Vidal et al., 2000]. The role of the DA-system for the Ne is supported by findings of a reduced Ne in Parkinson's disease (PD) [Falkenstein et al., 2001] and patients with basal ganglia lesions [Ullsperger and von Cramon, 2006]. In contrast, the Pe [Falkenstein et al., 2000; Leuthold and Sommer, 1999; Nieuwenhuis et al., 2001; for a Pe review see Overbeek et al., 2005] was not changed in PD, which suggests that it does not depend on the DA system.

In this study we assess the modulation of different levels of error processing (Ne and Pe) across the two stages of HD: the symptomatic (HD) and the presymptomatic stage (pHD). This is done to gain further insight into the processes that might mediate a possible deterioration of error feedback monitoring in HD compared to pHD [compare: Smith et al., 2000] on a neurophysiological and neuroanatomical level.

As stated in the model by Holroyd and Coles [2002] the basal ganglia and the ACC form a network, which generates the Ne [Carter et al., 1998]. Apart from the primary basal ganglia deficit also the ACC was found to show a dysfunction in HD [Bartenstein et al., 1997; Reading et al., 2004; van Dellen et al., 2001]. Besides grey matter, white matter also changes in HD [Beglinger et al., 2005; Fennema-Notestine et al., 2004; Paulsen et al., 2006] might

affect structures relevant to the generation of the Ne [Ullsperger and von Cramon, 2006], and might therefore be relevant to error processing. Therefore, the question arises if degeneration of grey matter or rather of white matter is functionally related to error processing in HD. This question can be examined using optimized voxel-based morphometry (VBM) [Ashburner and Friston, 2000, 2001; Good et al., 2001] in correlation with Ne as an indicator of error processing. The VBM is a useful tool to characterize subtle changes in brain structures [Mechelli et al., 2005], with the additional advantage that the MRI can be analyzed with respect to other parameters [Kassubek et al., 2005; Peinemann et al., 2005], like ERP-parameters [Araki et al., 2005]. On the basis of this, we derived the following hypothesis: (1) Since, the Ne is most likely reliant on the DA system (for review see Holroyd and Yeung, 2003), it should be reduced in HD compared to asymptomatic gene mutation carriers (pHD) because of less dopamine receptor expression at this stage [Augood et al., 1997; Backman et al., 1997]. (2) If the Pe also relies on the DA system, a similar effect would be expected for Pe. (3) As far as the degeneration in HD involves structures relevant to the processing of errors, a relation of the Ne, and volumetric abnormalities in these structures should be detectable.

In summary, the present study investigates changes of error-related ERP components (Ne and Pe) in patients with HD as compared with asymptomatic gene-mutation carriers (pHD) on a neurophysiological-neuroanatomical level.

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 [Huntington Study Group, 1996]. Besides these, a group of 12 right-handed presymptomatic gene mutation carriers defined a positive gene tests and absence of specific motor symptoms (pHD) ($N = 12$) from 24 to 56 years of age ($M = 35.91$; $SD = 9.30$) were recruited. Testscores and parameters of clinical relevance including differences between the groups (e.g. CAG-repeat, UHDRS, TFC, BDI, YMRS) are given in Table I. All patients and pHD's, accepted to be videotaped to document their neurological status. Neurological assessment in the pHD-group revealed no symptoms specific for HD.

Both patient groups had a comparable educational background. All participants gave written informed consent. The study was approved by the ethics committee of the University of Bochum.

Task

To measure error-processing we used a "Flanker Task" [Kopp et al., 1996], which reliably yields a high percentage of errors. Here vertically arranged visual stimuli were pre-

TABLE I. Clinical parameters (Age, Sex, CAG, BDI, YMRS, MMSE, UHDRS (motor), UHDRS (cognitive), TFC) compared between the pHD- and HD-group

Parameter	HD-group	pHD-group	Sig.
Age	38.22 (9.14)	35.91 (10.03)	ns
Sex	5 males/ 4 females	6 males/ 5 females	
CAG	46.11 (4.70)	42.58 (1.78)	$P = 0.27$
BDI	5.44 (4.03)	6.83 (6.61)	ns
YMRS	5.33 (5.31)	1.33 (1.37)	$P = 0.21$
MMSE	27.77 (2.33)	29.95 (0.86)	$P = 0.057$
UHDRS	25.44 (9.03)	0.81 (1.2)	$P < 0.001$
(motor)			
UHDRS	187.55 (69.48)	236.50 (16.81)	$P = 0.029$
(cognitive)			
TFC	12	13	$P < .001$

sented on a PC monitor. The target-stimulus (white arrowhead or circle) was presented in the center of a black background with the arrowhead pointing to the right or left. These target-stimuli were flanked by two vertically adjacent arrowheads, which pointed in the same (compatible) or opposite (incompatible) direction of the target stimulus. The flankers preceded the target by 100 ms to maximize premature responding to the flankers, which would result in errors in the incompatible and Nogo condition. The target was displayed for 300 ms. The response-stimulus interval was 1600 ms. Flankers and target were switched off simultaneously. Time pressure was administered by asking the subjects to respond within 550 ms, which additionally enhances the likelihood of errors. In trials with reaction times exceeding this deadline a feedback stimulus [1000 Hz, 60 dB sound pressure level (SPL)] was given 1200 ms after the response; this stimulus had to be avoided by the subjects. Four blocks of 105 stimuli each were presented in this task. Compatible (60%) and incompatible stimuli (20%), and Nogo-stimuli (circle) (20%) were presented randomly. The subjects had to react with the thumb depending on the direction of the central arrowhead and to refrain from responding to circles.

EEG Acquisition and Analysis

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 (sampling rate: 500 Hz). Cz was used as primary reference. The filter bandwidth was from DC to 80 Hz. Impedances were kept below 5 k Ω . The EEG was digitally filtered using a 0.10 Hz high-pass and 20 Hz low-pass filter. From the EEG response-locked ERPs were computed, beginning 400 ms before and ending 700 ms after the correct or incorrect response. After this, eye movement artifacts were corrected with the Gratton-Coles-Algorithm using the EOG data [Gratton and Coles, 1983], followed by

a baseline correction [from -200 to 0 ms (i.e. response)]. Remaining artifacts were rejected using an amplitude criterion of $\pm 80 \mu\text{V}$ followed by re-referencing all data to linked mastoids. The Nogo trial data were not further evaluated within the present study, which focused on error processing and not on inhibition. The amplitude of the Ne in error trials and of the CRN in the correct trials was measured relative to the peak of the positivity, which precedes both components [Falkenstein et al., 2000; Gehring and Knight, 2000; Kopp et al., 1996] at the electrodes Fz, FCz, and Cz. The Pe was measured by the mean deviation from baseline at electrode Pz (the maximum of the Pe) in the time interval from 200 to 500 ms postresponse in error as well as in correct trials. For the electrophysiological data the mean (M) and standard error of the mean ($\pm$ SEM) are given. For further statistical analyses a repeated measures ANOVA with the factor "electrode" (Fz, FCz, Cz) and "correctness" (correct vs. false responses) as within-subject factor and "group" (HD vs. pHD) as between-subject factor was calculated. For the Pe a repeated measures ANOVA with the factor "correctness" (correct vs. false responses) as within-subject factor and "group" (HD vs. pHD) as between subject factor was calculated.

MRI Acquisition

High resolution T1-weighted MRI (whole brain coverage, resolution $0.5 \times 0.5 \times 0.5 \text{ mm}^3$, TE = 3.4 ms, TR = 7.5 ms, flip angle 9° , FOV 256×256) were acquired on a 3 Tesla whole body scanner (Intera T 3.0, Philips, Best, NL), equipped with master gradients (nominal gradient strength 30 mT/m, maximal slow rate 150 mT/m/ms). A circularly polarized transmit/receive birdcage head coil with an HF reflecting screen at the cranial end was used for spin excitation and resonance signal acquisition. Sagittal slices (320) oriented to the AC-PC line were acquired.

Optimized VBM Analysis

Structural MRI data were processed using the optimized VBM method described by Good et al., [2001]. Image analysis was performed using the SPM2 software package (www.fil.ion.ucl.ac.uk/spm).

Image preprocessing

The optimized VBM procedure as described by [Good et al., 2001] consists of an iterative segmentation procedure to increase segmentation accuracy [Good et al., 2001]. A whole brain T1 template was created from all patients MRI data included in the study. The individual MRI images were transformed to match the Montreal Neurological Institute (MNI) T1 standard template applying a 12-parameter affine transformation in a Bayesian framework. The normalized images were segmented into grey matter, white matter, and cerebrospinal fluid (CSF) images and

smoothed with the default value full-width at half-maximum Gaussian kernel. Average images from the normalized grey matter, white matter, and CSF images were created and smoothed for use as own priors in the following steps.

In a second step normalization parameters are derived to transform segmented grey matter images in native space to the segmented own grey matter template. The original MR images were segmented into grey and white matter and nonbrain voxels removed. The extracted grey matter images were then normalized to the grey matter template created in step 1.

In a third step, the normalization parameters were then reapplied to the original whole-brain T1 images. These image volumes were resliced to isotropic voxels ($1 \times 1 \times 1 \text{ mm}^3$) and segmented into grey matter, white matter, and CSF. To compensate for the possible volume changes due to the spatial normalization procedure, the segmented images were modulated by the Jacobian determinants derived from the spatial normalization step. For statistic analysis, all segments were smoothed with a Gaussian kernel in the size of the expected effects (9 mm).

Statistical analysis of VBM

The normalized, segmented, modulated, and smoothed grey and white matter images were analyzed using SPM2. A correlation was calculated between the ERP amplitudes that showed significant results in the electrophysiological data analysis due to false responses at Fz and modulated grey or white matter volume. To adjust for global brain volume differences, total grey and white matter volume was included as covariate of no interest. Simple regression (correlation) implemented in SPM2 was used as basic model. To adjust for global brain volume differences, total grey or white matter volume, respectively, was included as covariate of no interest. An absolute threshold of 0.2 was applied. During optimized VBM, each voxel is given a probability of being gray or white matter or csf, the sum of the probabilities is 1. Absolute thresholding with 0.2 excludes those voxels from further analysis that show a probability of less than 0.2 (= 20%) of being the tissue type in question. This is a conservative approach excluding uncertain voxels. The main advantage is the avoidance of errors due to inverse correlations of tissue classes at borders between tissue classes, e.g. the probability of white and gray matter are inversely correlated at the border between gray and white matter. Changes in gray matter therefore affect the probability of white matter. Statistic parametric maps were thresholded at a probability (P) value of <0.001 uncorrected for multiple comparisons with an extent threshold looking for clusters with ≥ 100 contiguous voxels. For the analysis of potentials of the Fz-electrode, measuring the Ne-component, analysis was done for areas anterior of the brainstem coronar section (MNI coordinate $y > -10$). This was done, since the Ne is known to be elicited by frontal networks, especially the "rostral cingulate zone" [Ridderinkhof et al.,

2004]. The anatomical localization of significant brain regions was determined using the MNI space utility (MSU; www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html).

RESULTS

Behavioral Data

For the correct reactions (c-RT) reaction times differed between the groups [$F(2,19) = 11.41$; $P = 0.003$]. The HD group showed slower reaction times ($RT = 408.48 \text{ ms}$; $SD = 50.90$) than the pHD-group ($RT = 343.86 \text{ ms}$; $SD = 35.71$). With respect to the false reactions the groups did not significantly differ (HD: $RT = 317.01 \text{ ms}$; $SD = 58.54$) (pHD: $RT = 276.80 \text{ ms}$; $SD = 45.26$) [$F(1,19) = 3.16$; $P = 0.091$]. The groups did not differ with respect to the frequency of errors (HD: $M = 21.55$; $SD = 10.38$) (pHD: $M = 23.00$; $SD = 8.19$) [$F(1,19) = 0.16$; $P = 0.687$].

RTs of correct responses after an error has been committed (post RT) can be used to assess the behavioral consequences of an error. Therefore, we subjected the mean reaction time of all correct responses and those after an error as within-subject factor to a repeated measure ANOVA with group as between-subject factor. Post RTs ($390.46 \pm 12.34 \text{ ms}$), were significantly longer than c-RTs (375.66 ± 9.41) [$F(1,19) = 7.84$; $P = 0.011$]. No significant interaction with the factor group was obtained [$F(1,19) = 1.45$; $P = 0.242$]. Also the error correction rate did not differ between the groups (HD: $M = 4.33$; $SD = 3.70$) (pHD: $M = 7.08$; $SD = 9.53$) [$F(1,19) = 0.71$; $P = 0.407$].

ERP Data

The electrophysiological data were analyzed separately for the Ne and the Pe. The Ne amplitudes were analyzed in a repeated measures ANOVA with the factors "electrode" (Fz, FCz, Cz) and "correctness" (right vs. false reaction) as within-subject factors and "group" (HD vs. pHD).

The response-related negative potential differed significantly between the electrodes [$F(2,38) = 54.11$; $P < .001$]. Response-related negativities were larger at Fz ($-7.78 \pm 0.78 \mu\text{V}$) and FCz ($-9.03 \pm 0.72 \mu\text{V}$) compared to Cz ($-4.06 \pm 0.45 \mu\text{V}$). Fz and FCz did not differ from each other ($P = 0.064$). Furthermore the groups differed with respect to the activity at the different electrodes, as reflected in a group by electrode interaction [$F(2,38) = 5.55$; $P = 0.008$]. As expected, brain potentials differed between correct and false reactions [$F(1,19) = 75.55$; $P < 0.001$]. This effect differed between groups as reflected in a group by correctness interaction [$F(1,19) = 6.62$; $P = 0.019$]. A subsequent simple effects analysis revealed that the factor group was significant for errors [$F(1,19) = 12.47$; $P = 0.002$] but not for correct reactions [$F(1,19) = 3.96$; $P = 0.098$]. A separate ANOVA of the Ne (i.e. false reactions) at electrode Fz showed that the Ne was much smaller in manifest HD ($-7.81 \pm 2.35 \mu\text{V}$) than in pHD ($-14.44 \pm 5.49 \mu\text{V}$) [$F(1,19) = 11.38$; $P = 0.003$] ($\eta = 0.381$) (Fig. 1). Similar directed

Figure 1.

Grand averages of the Ne and CRN/Nc separated for the HD and pHD group at electrode Fz. Negativity is plotted downward, positivity is plotted upward. Shortly after the response, set at 0 ms, negative deflections are seen. It is shown that the Ne of the HD-group (black line) is attenuated compared to the pHD-group (blue line). No group differences in the CRN/Nc (green and grey line) are seen. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

effects, but smaller effect-sizes were seen at FCz (HD: $-9.28 \pm 3.52 \mu\text{V}$) (pHD: $-16.28 \pm 5.94 \mu\text{V}$) [$F(1,19) = 9.85$; $P = 0.005$] ($\eta = 0.339$), and Cz (HD: -3.42 ± 0.97) (pHD: -6.03 ± 2.40) [$F(1,19) = 9.30$; $P = 0.007$] ($\eta = 0.329$).

The ERPs at Pz are shown in Figure 2. Here a repeated measures ANOVA including the within-subject factor "correctness" (correct vs. false) with the between-subject factor group was calculated. As in case of the Ne correct-response potentials differed from false-responses potentials [$F(1,19) = 9.70$; $P < 0.001$] with false reactions showing a positive deflection ($3.84 \pm 1.11 \mu\text{V}$), the Pe, and correct reactions rather showing a broad negative deflection

($-1.98 \pm 0.64 \mu\text{V}$). This effect differed between groups as reflected in a group by correctness interaction [$F(1,19) = 9.70$; $P = 0.006$]. A subsequent simple-effects ANOVA revealed that this interaction was driven by the correct responses, which differed between groups [HD: $-0.27 \pm 0.98 \mu\text{V}$] (pHD: $-3.27 \pm 0.85 \mu\text{V}$) [$F(1,19) = 7.03$; $P = 0.016$]. A slow negativity is seen, which was much larger in the pHD-group compared to the HD-group. The error positivity in the error trials (Pe) did not significantly differ between the groups [$F(1,19) = 1.60$; $P = 0.221$] (HD: $2.43 \pm 1.68 \mu\text{V}$) (pHD: 5.25 ± 1.45) [$F(1,19) = 1.60$; $P = 0.221$] (Fig. 2).

Figure 2.

Grand averages of the Pe and the negativity related to corrected responses separated for the HD and pHD group at electrode Pz. Negativity is plotted downward, positivity is plotted upward. The response is set at 0 ms. In a time window from 200 till 500 ms a positive deflection in error trials (Pe) is seen in the HD (black line) and pHD group (blue line) not differing between the groups, despite the maps show a different topography. For correct reactions group differences are seen. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Voxel-Based Morphometry

Optimized VBM was used to (i) compare the presymptomatic and the symptomatic group and (ii) to investigate correlations of any white and grey matter voxels with the Ne amplitude of the electrode showing highest effect sizes in the electrophysio-

logical assessments (Fz). The comparison of the symptomatic and asymptomatic group revealed a significant difference mainly in the caudate nucleus (see Table II and Fig. 3).

The correlations of grey and white matter volume with the Ne amplitude over FZ revealed the following results:

TABLE II. Differences in grey matter volume between symptomatic and asymptomatic patients with Huntington's Disease

Anatomical location	Brodman area	MNI coordinate	Cluster size	Z-score
Left caudate		-13, 0, 15	572	5.23
Left thalamus		-4, -5, -1	3483	4.84
Left parahippocampal gyrus	BA 27	-14, -36, 1	166	4.47
Right parahippocampal gyrus	BA 19	25, -48, -7	598	4.31
Right posterior cingulate, and cuneus	BA 30	16, -68, -7	444	4.14
Right cuneus	BA 18	3, -94, 19	140	4.09
Right postcentral gyrus	BA 1, 3	64, -21, 34	148	3.94
Right cerebellum, anterior lobe, culmen		13, -40, -8	269	3.94
Left middle occipital gyrus	BA 19	-33, -88, 12	154	3.75
Left posterior cingulate	BA 30	-17, -62, 9	118	3.51

For grey matter volume, a region within the medial frontal gyrus significantly correlated with the Ne amplitude over FZ (Brodmann area BA 9, coordinate 6, 45, 26, cluster size 130, $T = 14.27$, Z-score 4.48, $P < 0.001$ uncorrected for multiple comparisons) (Fig. 4). For presymptomatic patients, there was no significant correlation.

Regarding the white matter, no correlation was found for the symptomatic and asymptomatic group. These pattern of results remained stable even when another kernel-size for smoothing was used.

DISCUSSION

In the current study we examined levels of error processing at different stages of HD to gain more insight into the processes that might mediate a distortion of error processing in HD compared to pHD as described by Smith et al., [2000] on a neurophysiological and neuroanatomical level. However, in some cases it is difficult to distinguish between symptomatic and presymptomatic HD. Personality changes [Kirkwood et al., 2002] and subtle cognitive changes as well as unspecific motor deficits may precede the manifest onset of disease [Kirkwood et al., 2000]. Since this is an intense matter of debate, it is difficult to differentiate between these unspecific alterations and specific alteration, which are needed for clinical diagnosis of symptomatic HD. However, in our study the presymptomatic phase of disease is defined by absence of specific motor

Figure 4.

The grey matter volume in the right medial frontal gyrus (BA 9) revealed a significant correlation with the Ne potential over electrode FZ for the HD-group. The results are displayed on the averaged brain of all patients included in this study ($N = 21$). The color bar represents T-values. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 3.

Differences in grey matter volume between symptomatic and asymptomatic HD patients as detailed in Table II. (independent-sample t -test, $P < 0.001$ uncorrected for multiple comparisons, $k = 20$). The color bar represents T-values. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

symptoms. A comparison of the groups (HD and pHD) using VBM revealed differences in grey matter volume in the caudate nucleus, which is the main manifestation of disease and disease progression occurs mainly in this anatomic region. This group difference could result from ventricle shape differences and brain atrophy.

With respect to the early components associated with performance monitoring (Ne and Nc/CRN) we found that the groups (HD and pHD) differed with respect to the amplitude of the Ne (i.e. false responses). The HD group showed a reduced Ne amplitude compared to the pHD group. The amplitude reduction of Ne proved to be specific for error trials, i.e. for the Ne, since the Nc/CRN showed no group differences. According to the late parietal ERP(s) concerning performance monitoring (Pe) the opposite pattern was found. The Pe did not differ between the groups, but the potentials on correct responses did. The results of the VBM using the amplitude values of the Ne showed that the Ne was related to neuroanatomical changes.

Behavioral Data

The behavioral data indicate that both groups committed a comparable amount of errors. Thus, the group differences in the ERP are unbiased because of the frequency of errors, which could have influenced the results. Even though the Ne was reduced in the HD compared to the pHD group, both groups did not differ in their error

correction rate and posterror slowing, indicating that behavioral adaptation is possible even with a reduced Ne. Interestingly, also healthy elderly subjects show a clear Ne reduction [e.g. Band and Kok, 2000; Falkenstein et al., 2001], while their posterror slowing is generally not reduced, but rather enhanced, compared to young controls [Band and Kok, 2000; Falkenstein et al., 2001]. Hence both results suggest that behavioral adaptation can be triggered already by the existence of an Ne, while the strength of the Ne seems less important.

Ne

The Ne has consistently been shown to depend on the DA system [Bates et al., 2004; Falkenstein et al., 2001; Liotti et al., 2005; Ridderinkhof et al., 2002] [for review see Holroyd and Yeung, 2003]. The effect of the reduced Ne for HD—compared to pHD—patients might therefore be attributed to the enhanced dopamine pathology in manifest HD compared to the preclinical phase (pHD) [Augood et al., 1997; Backman et al., 1997; Turjanski et al., 1995]. The results are in line with the reinforcement learning hypothesis stating that the dopamine system is crucial for error-processing [Holroyd and Coles, 2002]. In addition to the importance of dopamine, the model proposed by Holroyd and Coles [2002] states that the basal ganglia detect a mismatch between the expected and actual outcome of an event (e.g. a response) and sends an error signal to the ACC, which in turn elicits the Ne, implying that the basal ganglia and the ACC are functionally connected. The results of the VBM revealed that the Ne amplitude at Fz (showing the largest effect size in group difference) was related to the grey matter at BA 9 at the transition to the “rostral cingulate zone” [Fiehler et al., 2004], encompassing BA 24 (ACC) and BA 32. No relation was found in pHD. The “rostral cingulate zone” is supposed to play an important role in the generation of the Ne [for review: Ridderinkhof et al., 2004; Fiehler et al., 2004]. As stated in the introduction the ACC was found to show a dysfunction in HD as can be seen in a PET-study assessing central motor functioning [Bartenstein et al., 1997], an fMRI-study assessing performance in an interference paradigm [Reading et al., 2004], and an animal study about neural transplantation [van Dellen et al., 2001]. Our results extend these findings, showing that another area of the medial frontal cortex is also dysfunctional in HD. The fact that we did not find a relation in the pHD-group may be due to the fact that it is either not damaged at this stage, or damage is so subtle that it is beyond sensitivity of our MRI measurement. However, we were not able to find a relation to the white matter [Ullsperger and von Cramon, 2006] in single-group analysis, suggesting that possible damage to the white matter shown to be of importance for cognitive functions in HD [Beglinger et al., 2005; Fennema-Notestine et al., 2004; Paulsen et al., 2006] is not of importance to processes related to performance monitoring deficits in HD. In summary, these results suggest that the difference

in the Ne between our two patient groups possibly rely on two factors: (i) the DA alteration, which is most likely more expressed in the HD-group and (ii) the grey matter of the rostral cingulate zone (BA 9) [Ridderinkhof et al., 2004]. How do these findings may relate to each other? It may be hypothesized that both factors have additive effects on the Ne-modulation: As such the more expressed DA dysfunction in HD compared to pHD may cause a reduction in the mismatch-detection process between the neural representations of the actual erroneous response and the planned correct response [Falkenstein et al., 1991; Gehring et al., 1993]. This error signal, which is supposed to be conveyed from the basal ganglia to the ACC [Holroyd and Coles, 2002] may be further attenuated in HD by the structural differences of the grey matter (BA 9). However, since HD is a disorder that is accompanied by a widespread neuropathology [for review see Gutekunst et al., 2002] and by changes in multiple neurotransmitter systems [for review see Yohrling and Cha, 2002] it cannot be ruled out that changes in the other neurotransmitter systems have an additional effect and might therefore also modulate the Ne.

Pe

The analysis of the late components of error processing revealed that the error positivity (Pe) did not differ between the groups. Since in HD the DA system is predominantly affected [Augood et al., 1997; Backman et al., 1997; Ginovart et al., 1997; Turjanski et al., 1995], this effect suggests that the Pe is not dependent on the DA system, which is in line with previous findings in PD [Falkenstein et al., 2005] and psychiatric diseases affecting the dopamine system such as schizophrenia [Alain et al., 2002; Bates et al., 2004; Ford, 1999]. The distribution and latency of the Pe is similar to the well-known P3, which has also been shown to be unrelated to DA functioning [for review see Frodl-Bauch et al., 1999].

Though the Pe did not differ, a group difference was seen in correct trials. Since, this negativity precedes the next imperative stimulus one may assume this potential to reflect a “contingent negative variation” (CNV) [Verleger et al., 1999; Walter et al., 1964], which is prominent at Pz in choice reaction tasks [Lorist et al., 2000]. Since, the CNV most likely relies on the DA system [Amabile et al., 1986; Cunningham et al., 2001; Pulvermüller et al., 1996; Verleger et al., 1999] the observed group difference in our slow negativity might also be due to the stronger DA dysfunction in HD compared to pHD. This issue of possible CNV decrements in HD vs. pHD will be pursued in a different study focused on preparatory processes.

CONCLUSION

Overall, the present results show that presymptomatic and symptomatic patients with HD differ in a brain potential most likely depending on the dopamine system: the error negativity (Ne). Hence our results show deficits in

error detection in patients with manifest HD compared to preclinical patients. These deficits are not reflected in overt behavior, which shows the additional value of the ERPs to detect covert cognitive changes. Moreover, the changes of the Ne were related to specific structural changes of the grey matter at BA 9. The results demonstrate how deterioration in error-processing in HD [Smith et al., 2000] might be mediated on a neurophysiological and neuroanatomical level.

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