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ORIGINAL ARTICLE

Evidence for divergent effects of neurodegeneration in Huntington's disease on attentional selection and neural plasticity: implications for excitotoxicity

Christian Beste · Ann-Kathrin Stock ·
Vanessa Ness · Rainer Hoffmann · Carsten Saft

Abstract It is generally assumed that neurodegeneration leads to declines in cognitive functions. However, there is evidence that neurodegenerative processes related to excitotoxicity can lead to paradoxical improvements in circumscribed cognitive functions, while at the same time other processes are compromised. An open question is how such paradoxical improvements reported in literature and declines usually associated with neurodegeneration relate to each other. Do paradoxical improvements only reflect a transient phenomenon, or do they intensify in the course of neurodegeneration? We examine this question using behavioral and neurophysiological (EEG) data in a human model of excitotoxic neurodegeneration (i.e., Huntington's disease, HD). The results show that attentional selection processes decline during pre-manifest disease progression. Importantly, the efficacy of protocols used to induce neural plasticity in processes underlying attentional selection processes also increases in course of ongoing neurodegeneration in pre-manifest HD. This was reflected in behavioral data and electrophysiological correlates of processes related to the allocation of attention. To conclude, our results suggest that circumscribed enhancements of specific cognitive functions are as much a result of the developmental process of neurodegeneration as the well-known detrimental effects. The results account for the divergent effects of neurodegenerative processes closely related to excitotoxicity on cognitive functions.

Keywords Neural plasticity · Neurodegeneration · Excitotoxicity · EEG · Huntington's disease · Attention

Introduction

Excitotoxicity plays a major role in various neurodegenerative diseases, leading to declines in cognitive functions (Milnerwood et al. 2010; Okamoto et al. 2009; Tabrizi et al. 2009; Beal and Ferrante 2004). One of these diseases, besides other pathophysiological mechanisms associated with excitotoxicity, is Huntington's disease (HD) (Milnerwood et al. 2010; Okamoto et al. 2009).

NMDA receptors mediating excitotoxicity play an ambivalent role (Cardoso-Leite et al. 2012; Hardingham and Bading 2010). It has been demonstrated that exaggerated glutamatergic neural transmission induces neurodegenerative effects and weakens structural integrity of brain tissue (e.g., Hardingham and Bading 2010). However, in HD as a possible model to study the effects related to excitotoxicity, it has also been suggested that excitotoxicity leads to paradoxical efficiency increases in some cognitive functions that are strongly dependent upon glutamatergic neural transmission (Beste et al. 2008a, 2012). It has been suggested that, as a consequence of excitotoxicity, mechanisms of neural plasticity and long-term potentiation-like processes, which are known to

C. Beste (✉) · A.-K. Stock
Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, TU Dresden, Schubertstrasse 42, 01309 Dresden, Germany
e-mail: christian.beste@uniklinikum-dresden.de

V. Ness
Institute for Cognitive Neuroscience, Biopsychology, Ruhr-University, Bochum, Germany

R. Hoffmann · C. Saft
Department of Neurology, Huntington Centre NRW, St. Josef Hospital, Ruhr-University, Bochum, Germany

depend upon glutamatergic neural transmission (e.g., Abraham and Williams 2003; Bi and Poo 2001), become more efficient (Beste et al. 2011, 2012).

However, an open question is if the above-mentioned paradoxical improvements occurring during neurodegeneration in HD only reflect a transient phenomenon. Some results on sensory memory and attentional processes suggest that increased performance, possibly due to excitotoxicity in HD, only emerges in the manifest stage and hence in a state where neurodegenerative processes have progressed (Beste et al. 2008a). It is therefore possible that paradoxical improvements increase in strength as (pre-manifest) disease progresses. This has never been directly tested on the basis of longitudinal data. Such a result would suggest that the paradoxical neurodegenerative effects in HD, attributable to processes of excitotoxicity, also increase in their effects on cognitive functions, as it is well-known for the detrimental effects.

If these paradoxical efficiency increases of neural plasticity processes reflect an aspect of ongoing excitotoxic neurodegeneration, a longitudinal examination of neural plasticity processes in a disease associated with excitotoxicity (like HD) may reveal that neural plasticity processes show increases in their efficacy as the disease progresses. However, excitotoxicity also compromises the structural integrity of neuronal networks. We, therefore, hypothesize that excitotoxic neurodegeneration is characterized by divergent developmental trajectories.

To examine this question we conducted a longitudinal study in pre-manifest HD gene mutation carriers as disease model associated with excitotoxic neurodegeneration. To investigate possible divergent effects of ongoing excitotoxic neurodegeneration, we induced neural plasticity to modulate attentional selection processes by means of "training-independent sensory learning" (TISL), a novel method to induce neural plasticity effects (Beste and Dinse 2013). This process has been shown to be more efficient in excitotoxicity (Beste et al. 2012), likely because NMDA receptor-mediated neural transmission has been shown to modulate TISL (Dinse et al. 2003). We used EEG to examine the neurophysiological processes underlying the longitudinal modulation of these effects. Using EEG, event-related potentials (ERPs), recorded at parieto-occipital electrodes, were utilized as markers for the spatial allocation of attention (Eimer and Kiss 2008).

As a consequence of the ambivalent effects of excitotoxic neurodegeneration, we expected the attentional selection processes to show declines during longitudinal examination. However, we also expected a concomitant increase in the efficacy of TISL to modulate attentional selection processes, as a consequence of ongoing excitotoxicity processes.

Materials and methods

Participants

Twenty-nine ($n = 29$), right-handed pre-manifest HD gene mutation carriers were examined at baseline. Over a 21-month period, three pre-HD subjects dropped out because of personal reasons. A total of 26 pre-manifest HD gene mutations were analyzed across all time-points. The classification of "absence of clinical motor symptoms" (i.e., pre-manifest stage) was based on expert raters' assessments of motor signs that were not sufficient for the diagnosis of HD (Diagnostic Confidence Level, item 17 of the UHDRS Motor Assessment) (Huntington Study Group 1996). Two out of these 26 pre-manifest HD subjects revealed pheno-conversion in the 21-month period, i.e., they developed manifest motor symptoms. The pre-HD participants showed no other comorbid disorders and were free of brain injury.

All pre-HD participants underwent neurological assessment and were scored according to the UHDRS items "motor scale" (MS), "total functional capacity", "independence scale" (IS), and the items verbal fluency test, symbol digit test, interference test, color naming, and word reading, which were summarized as "cognitive score" (CS) (Huntington Study Group 1996). For each pre-manifest participant, the probability of estimated disease onset (age of onset, AO) within 5 years was calculated according to Langbehn et al.'s (2004) parametric model. The expected AO was also estimated using the Langbehn's formula. Years to disease onset (YTO) for the pre-HD subjects was calculated by subtracting the subject's age at the time of investigation from his or her estimated onset age. We also calculated the "disease burden score" [DBS = (CAG repeat − 35.5) × age] for each subject, which denotes genetic disease load, corrected for the age of the subject (Tabrizi et al. 2009). As controls, a group of right-handed, healthy subjects case-matched to the pre-HD group in age, sex, educational status, and socio-economic background was enrolled in the study and investigated at all time-points. All participants gave written informed consent before any of the study protocols commenced. The demographical information and clinical data (mean ± SD) for the pre-HD groups for each time-point are presented in Table 1. The clinical parameters of the HD group receiving stimulation and no stimulation (see below) did not differ from each other. The study was approved by the Ethics Committee of the Ruhr-University Bochum, Germany. The study was conducted according to the Declaration of Helsinki.

Table 1 Clinical and demographical data of the examined cohorts

Parameter	Baseline		21-month	
	EBL	No EBL	EBL	No EBL
N	15	14	14[§]	12[§]
Age	40.4 (10.5)	36.93 (10.7)	42.1 (10.2)	38.63 (11.1)
Sex				
Female	9	7	8	6
male	6	7	6	6
CAG repeats	42.06 (2.49)	42.4 (2.44)	42.06 (2.49)	42.4 (2.44)
Disease burden score (DBS)	255.6 (85.89)	239.86 (70.11)	265.51 (91.23)	249.75 (73.43)
Years to onset (YTO)	16.24 (9.57)	17.16 (7.13)	14.49 (9.11)	15.41 (6.43)
UHDRS (motor score)	3 (2.61)	2.53 (2.58)	3.5 (3.81)	5.12 (4.99)
UHDRS (total functional capacity scale)	12.93 (0.25)	12.86 (0.35)	12.84 (0.37)	12.85 (0.36)
UHDRS (independent scale)	99 (2.07)	99.66 (1.29)	98.46 (3.75)	98.92 (2.89)
UHDRS (cognitive score)	329.80 (43.10)	332.20 (36.92)	339.23 (44.68)	344.42 (40.16)

[§] One subject in the "EBL group" and one subject in the "no EBL group" revealed phenoconversion, i.e., was diagnosed with manifest HD in the 15-month and 21-month endpoint. Excluding these subjects did not change the pattern of results observed for the behavioral and electrophysiological data. The results are therefore not biased by these two patients

Task

The task used was identical to those used in previous studies by our group and has been described in detail (Beste et al. 2011, 2012). The task is shown in Fig. 1.

In short, subjects were shown two vertically or horizontally oriented bars, presented 1.1° to the left and right of a fixation cross (refer Fig. 5). The bars were either darker or brighter than the background. In each trial, two frames
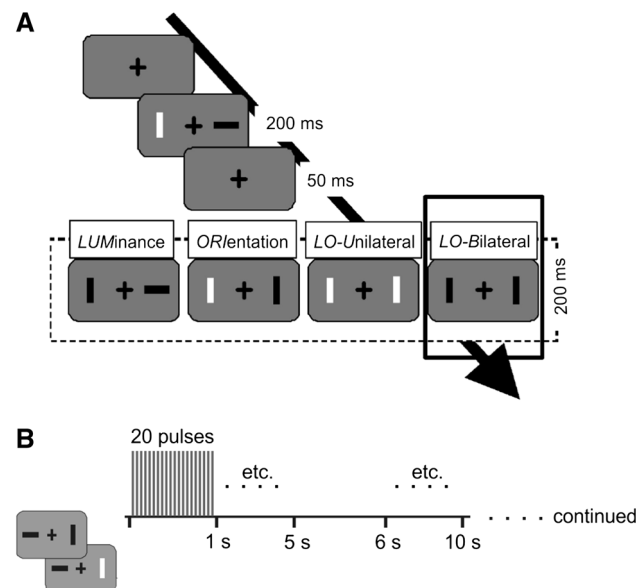

Fig. 1 a Schematic illustration of the attentional selection paradigm. **b** Schematic illustration of the stimulation protocol used to induce plasticity. Luminance changes are presented at a frequency of 20 Hz for 5 s, followed by an interval of 5 s with no stimulation. This was repeated for 20 or 40 min, depending on the group

of these stimuli were presented for 200 ms in rapid succession. For a short break of 50 ms between the appearances of the two frames, only the fixation cross was visible. Between the two frames, there were changes in the luminance of a single bar (LUM), the orientation of a single bar (ORI), both the luminance and the orientation of a single bar (LOU), or the luminance and orientation distributed across the two bars (competitive trials; LOB). The competitive trials condition (LOB) is specifically demanding because the participant's ability to detect a relevant luminance change is distracted by the irrelevant orientation change. TISL is specifically effective in this condition (Beste et al. 2011). The participants were required to detect changes in luminance and to ignore orientation changes, pressing a button with the index finger of the left or the right hand to signify the side on which the change appeared. If no change occurred, participants were required to refrain from pressing any buttons (Nogo trials). Overall, 512 trials were presented in a random order. The inter-trial interval varied from 2,000 to 2,500 ms. Responses were recorded from the onset of the second frame (change stimulus) until 1,500 ms after the occurrence of the second frame. Responses exceeding this time interval were categorized as "misses". Responses faster than 150 ms were categorized as "fast guesses". Response errors fell into two categories: incorrect button presses and false alarms (responses in the Nogo condition).

Induction of task-independent sensory learning

To induce perceptual learning, we used the same protocol that has been shown to produce robust learning effects (Beste et al. 2011). In all groups and for all longitudinal

time-points, performance in the competitive change detection task was assessed at two time-points: prior to stimulation (baseline) and after stimulation. To induce TISL (Beste and Dinse 2013), we applied an intermittent high-frequency stimulation protocol (LTP-like stimulation protocol) by presenting changes in the luminance of the bar stimuli on the right side of the fixation cross. During TISL, stimuli are presented at a pace resembling the timing properties of long-term potentiation (LTP) protocols used in cellular studies (Cooke and Bear 2011; Seitz and Dinse 2007; Frenkel et al. 2006). Changes in luminance (altering between 20 and 45 cd/m^2) occurred with a frequency of 20 Hz for a period of 5 s, followed by a period of 5 s with no presentation of luminance changes on the screen. During this period, the flickering bar was maintained in an upright orientation. On the left side, a stable bar was presented. It may be argued that the frequency used is quite low to induce LTP-like effects, since LTP is usually induced using frequencies higher than 50 Hz. However, at higher frequencies (>60 Hz) a stable picture will emerge because presentation is above flimmer-fusion-frequency. That is why we used a stimulation frequency of 20 Hz, also because such a frequency has been shown to be effective in other sensory modalities to induce training-independent sensory learning (for review: Beste and Dinse 2013). During TISL, changes in luminance were presented (see "Methods" section). TISL is performed in the right visual field to confine plasticity-induced changes in luminance detection within this field (Beste et al. 2011).

To force participants to attend to the fixation cross during LTP-like stimulation, 10 % of the trials during the stimulation procedure were catch trials (a trial was defined as a 5-s time span containing either flickering of luminance, or a blank screen). Catch trials occurred with equal frequency in periods with and without luminance changes. In these trials, the fixation cross was shifted out of the original position by a visual angle of 0.2°, and participants were asked to press a button whenever a catch trial occurred. The contrast of the stimuli used during LTP-like stimulation and the positioning of the stimuli on the monitor were identical to the competitive change detection task paradigm.

The exposure time used for the LTP-like stimulation protocol was similar to the baseline study (cf. Beste et al. 2012). For the baseline study, pre-HDs were randomly divided into two subgroups: one pre-HD subgroup ($n = 14$) received no stimulation between the first and second measurement of performance in the competitive change detection task ("no stimulation pre-HDs"), and the other subgroup ($n = 15$) received 20 min of stimulation ("TISL pre-HD 20"). Twenty-minute TISL has been shown to induce robust plasticity effects in pre-HDs (cf. Beste et al. 2012). To keep the effects of TISL comparable

across longitudinal time-points, 20 min of TISL was also used for the 15-month and 21-month longitudinal endpoints. The assignment of pre-HDs in both subgroups for the baseline measurement was conducted under the constraint that the two subgroups did not differ from each other in clinically relevant or demographic parameters. For the longitudinal study, the distribution of pre-HD participants in the stimulation and non-stimulation groups was the same as for the baseline time-point. In addition, two groups of control participants were investigated. One group of control participants ($n = 15$) received no stimulation between the first and second measurements ("no stimulation control"). A second group of control participants ($n = 15$) received 40 min of stimulation ("LTP control group 40"). A control group receiving 20 min of stimulation was not used, since this group did not show TISL effects in a previous study (cf. Beste et al. 2012).

EEG recording and analysis

Recording and analysis of EEG data was identical to previous studies using this paradigm and to the baseline study (cf. Beste et al. 2012). Each electroencephalogram (EEG) was recorded from 64 Ag/AgCl electrodes distributed across the entire scalp, according to the extended 10/20 system. Electrode impedances were kept below 5 kΩ. The common average served as an online reference. Each EEG was sampled online with a frequency of 1 kHz by using a QuickAmp DC-amplifier (Brain Products, Inc.) applying a band-pass filter of 0–200 Hz during recording. The influence of eye movement on EEG activity was corrected using independent component analysis (Infomax algorithm). Some components were rejected upon visual inspection. Before the segmentation of the data, the EEG was re-referenced to linked mastoids and inspected for artifacts. Each segment had a length of 1,500 ms (from 250 ms before the onset of the first frame to 1,000 ms after the second frame). The baseline was set from −200 ms until the presentation of the first frame of the stimulus array (Wascher and Beste 2010). To examine visual-spatial processing, event-related lateralizations (ERLs) using electrodes PO7/PO8 were calculated. ERLs were calculated by subtracting the ipsilateral activity from the contralateral activity (Beste et al. 2012). In case of conflict trials, the target element (i.e., luminance change) served as a reference for the distraction. This procedure is comparable to the computation of the lateralized readiness potential (Wascher and Beste 2010). This subtraction procedure allows a "weighting" of the activity induced by changes of the visual feature on the left and right side of the stimulus display. It is therefore possible to weight the relative influence of the target (luminance change) and the distractor (orientation change). The polarity of the resulting ERL potential hence indicates the

spatial orientation of attention. Prior to TISL, attention is usually directed to the distractor (reflected by the N1pc ERP) and only subsequently shifted to the target stimulus (reflected by the N2pc ERP) (Beste et al. 2012; Wascher and Beste 2010; Eimer and Kiss 2008) when applying this task. After TISL, N1pc polarity changes (i.e., turns negative), indicating that attention is initially directed to the target stimulus (Beste et al. 2012).

In the current analysis and for the conflict condition (LOB), positive values denote an orientation of attention to the distractor and negative values denote an orientation of attention to the target (Wascher and Beste 2010). In non-conflict conditions (i.e., LUM, ORI, and LOU), activations in the N1-range denoting bottom-up driven activations of the sensory system were measured as a maximum of this asymmetry in the time interval between 140 and 240 ms over posterior electrodes. In the conflict condition (LOB), the asymmetry in the N1-range was measured as the mean amplitude in the time interval between 150 and 200 ms. The N2pc following the first response was measured in the time interval between 270 and 450 ms in the conflict condition only. The fronto-central N2 was measured in the same interval in the conflict condition.

Statistical analyses

Behavioral and ERP data were analyzed using repeated-measures ANOVAs (GLMs), including the within-subject factors "type of change" (LUM, LOU, LOB), "test session" (pre-TISL, post-TISL), "time-point" (i.e., baseline, 21 month), and "side" (left vs. right target presentation). The factor "group" was used as a between-participant factor. There were four groups: "no stimulation pre-HDs", "TISL pre-HD 20", "no stimulation control", and "LTP control group 40". The factor "side" is introduced, because for the induction of TISL we used a unilateral stimulation protocol. That is, on in the right visual half field changes in luminance were presented in an LTP-like fashion. Previous studies revealed that under such condition, the plasticity effects are confined to stimuli in the hemifield used during stimulation (Beste et al. 2011). Stimulation in the right visual half field therefore leads to plasticity effects in the right, but not in the left visual half field. It is therefore important to account for this differential effect.

Because no response is required when only changes in orientation appear (ORI), this "Nogo condition" was analyzed separately to control for premature response tendencies. Greenhouse-Geisser correction was applied where appropriate, and calculated post hoc tests were Bonferroni-corrected. All variables and residuals included in the ANOVAs (GLMs) were normally distributed, as indicated by Kolmogorov–Smirnov tests ($z < 0.3$ for all; $p > 0.7$).

Results

Behavioral data

For the conditions for which no competition in attentional selection is evident (i.e., LUM, ORI, and LOU) (see "Methods" section), the behavioral data did not reveal significant effects of stimulation, groups, or longitudinal time-points (all $F < 1$; $p > 0.4$). The behavioral data for these conditions are shown in supplementary Table 1.

For targets (luminance changes) presented in the right visual field and in the most difficult attentional condition (the LOB condition) (see "Methods" section), there was an interaction of "pre-stimulation/post-stimulation × longitudinal time-point × group" for the accuracy of luminance change detection ($F(3,52) = 6.55$; $p = 0.004$; $\eta^2 = 0.22$). This interaction is shown in Fig. 2. Supplementary Figure 1 shows single-subject behavioral data.

To examine in greater detail the observed interactions for accuracy in the right visual field in the LOB condition, the control groups and pre-HD groups were analyzed separately. In the control groups this analysis revealed the following: Analyzing the pre-stimulation performance revealed no interaction of "time-point × group", no main effect of "group", and no main effect of "time-point" (all $F < 0.8$; $p > 0.6$). After TISL, a "group" effect was evident for behavioral performance ($F(1,28) = 206.08$; $p = 1 \times 10^{-7}$; $\eta^2 = 0.88$). These results showed that performance increased in the control group receiving 40 min of TISL compared with the control group receiving no TISL. The absence of any interaction with "time-point" within the behavioral data (all $F < 0.8$; $p > 0.4$) showed that this post-TISL pattern was evident at all time-points to the same degree.

This pattern differed in the pre-HD groups. Prior to TISL, the main effect of "time-point" in the behavioral data ($F(1,24) = 22.55$; $p = 1 \times 10^{-4}$; $\eta^2 = 0.69$) showed that performance in detecting luminance decreased across time-points (Fig. 2). The absence of "time-point × group" interactions (all $F < 0.2$; $p > 0.7$) showed that, prior to TISL, this effect was evident in both pre-HD groups. Importantly, a post-TISL interaction of "time-point × group" was evident in the behavioral data ($F(1,24) = 11.33$; $p = 0.004$; $\eta^2 = 0.30$). To explore this interaction, we calculated the degree of TISL effect as the difference between pre-stimulation and post-stimulation performance for each time-point. These data showed that the degree of learning differed across time-points. For the behavioral data (Fig. 2), the magnitude of learning in pre-HDs was larger at 21 months, compared to baseline ($p = 0.025$). The magnitude of learning at the 21-month time-point in pre-HDs was also larger ($p = 0.0001$) compared to that in controls, for which the magnitude of TISL
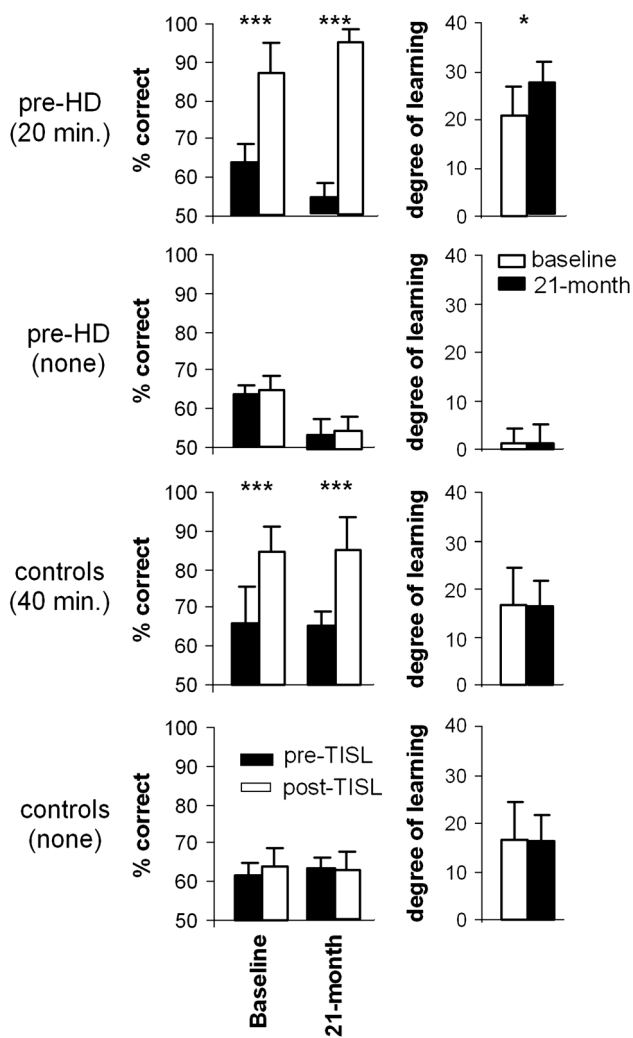
Fig. 2 Behavioral data for the baseline and 21-month endpoint. The left histograms illustrate the rate of corrected luminance identifications (mean ± SEM) in the LOB condition for the pre-TISL and post-TISL measurements for the different experimental groups. The right histograms illustrate the degree of learning for the *different* time-points in each experimental group

effects did not vary across time-points ($p > 0.8$). Comparing post-stimulation performance across time-points showed that post-stimulation performance was higher for the 21-month endpoint compared to baseline ($p = 0.033$). This means that the increased plasticity effect was not a simple effect of the decline observed in attentional performance prior to the induction of TISL.

Neurophysiological data

N1pc data

As with the behavioral data, the neurophysiological data did not reveal significant effects of stimulation, groups, or longitudinal time-points (all $F < 0.9$; $p > 0.4$) in

conditions for which no competition in attentional selection was evident (i.e., LUM, ORI, and LOU). The neurophysiological data for these conditions are shown in supplementary Figure 2.

Paralleling the behavioral data, there was an interaction effect for the N1pc ($F(3,52) = 5.77$; $p = 0.0001$; $\eta^2 = 0.31$). No such interaction was observed for the N1pc latencies (all $F < 2$; $p > 0.2$). Figure 3a shows the ERLs for right-sided luminance changes in the LOB condition for each longitudinal time-point before and after TISL induction. Figure 3b shows the degree of change between the pre-TISL and post-TISL measurements at each longitudinal time-point for each experimental group. Single-subject N1pc data are shown in Supplementary Figure 3.

Analyzing the pre-stimulation performance and the N1pc data in the two control groups revealed no interaction of "time-point × group", no main effect of "group", and no main effect of "time-point" (all $F < 0.5$; $p > 0.7$). This showed that behavioral performance and direction of attention prior to TISL did not vary across time-points in controls.

After TISL, a "group" effect was evident for the N1pc data ($F(1,28) = 55.11$; $p = 1 \times 10^{-5}$; $\eta^2 = 0.51$). The neurophysiological data (Fig. 3) suggested that performance increased, since attention was allocated not to the distractor but to the target, as indicated by the change in N1pc polarity after TISL (see "Methods" section). The absence of any interaction with "time-point" within the behavioral and neurophysiological data (all $F < 0.7$; $p > 0.4$) showed that this post-TISL pattern was evident at all time-points to the same degree.

This pattern differed in the pre-HD groups. Prior to TISL, there was a main effect of "time-point" for the N1pc data ($F(1,24) = 28.44$; $p = 2 \times 10^{-4}$; $\eta^2 = 0.49$). The N1pc became more negative across time-points, and all time-points differed from each other ($p < .001$). The absence of "time × group" interactions ($F < 0.5$; $p > 0.5$) showed that, prior to TISL, this effect was evident in both pre-HD groups. For the post-TISL data, and in line with the behavioral data, there was an interaction of "time-point × group" for the N1pc ($F(1,24) = 9.33$; $p = 0.003$; $\eta^2 = 0.22$). Calculating the degree of TISL effects, these data showed that learning effects differed across time-points. The magnitude of learning in pre-HDs was larger at the 21-month time-point compared to baseline ($p = 0.001$), as well as compared to controls ($p = 0.004$). In the pre-HD group receiving TISL, N1pc was more negative after TISL at the 21-month endpoint compared to baseline ($p = 0.009$). This paralleled the behavioral data and showed that increased plasticity effects were not only due to declines in attentional selection performance.
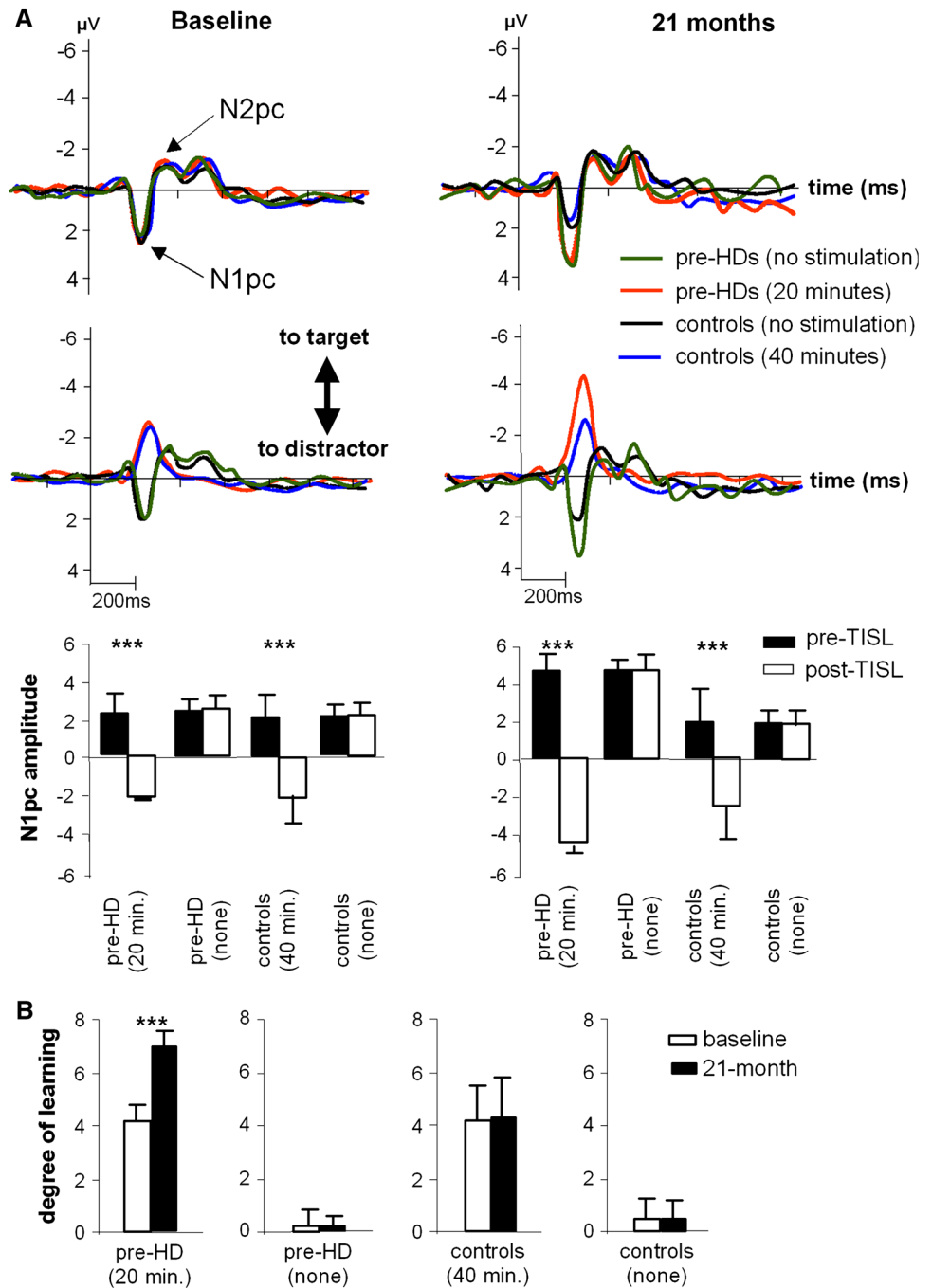
N2pc and fronto-central N2 data

In addition to the N1pc, we also evaluated the effects of disease progression and its interaction with the effects of TISL for the N2pc and the fronto-central N2. The N2pc reflects attentional re-allocation processes (Eimer and Kiss 2008), and the fronto-central N2 has been suggested to reflect conflict-monitoring functions (e.g., Folstein and van Petten 2008). Both processes have been shown to be involved in this task (e.g., Wascher and Beste 2010) and the fronto-central

N2 has been shown to be affected in HD and other disorders affecting the basal ganglia (Willemssen et al. 2011; Verleger et al. 2010; Nguyen et al. 2010). Attentional re-allocation processes are necessary to counteract the effects of a distractor. Conflict-monitoring processes are triggered by the perceptual competition between the target stimulus (luminance change) and the distractor stimulus (orientation change) (cf. Wascher and Beste 2010).

The N2pc is shown in Fig. 3. The analysis of the N2pc amplitude revealed no interaction of

Fig. 4 Electrophysiological data for the baseline and 21-month endpoint for the fronto-central N2 for each experimental group and each longitudinal endpoint for the 1st and the 2nd measurement (i.e., prior to and after EBL). The different experimental groups are *color-coded*
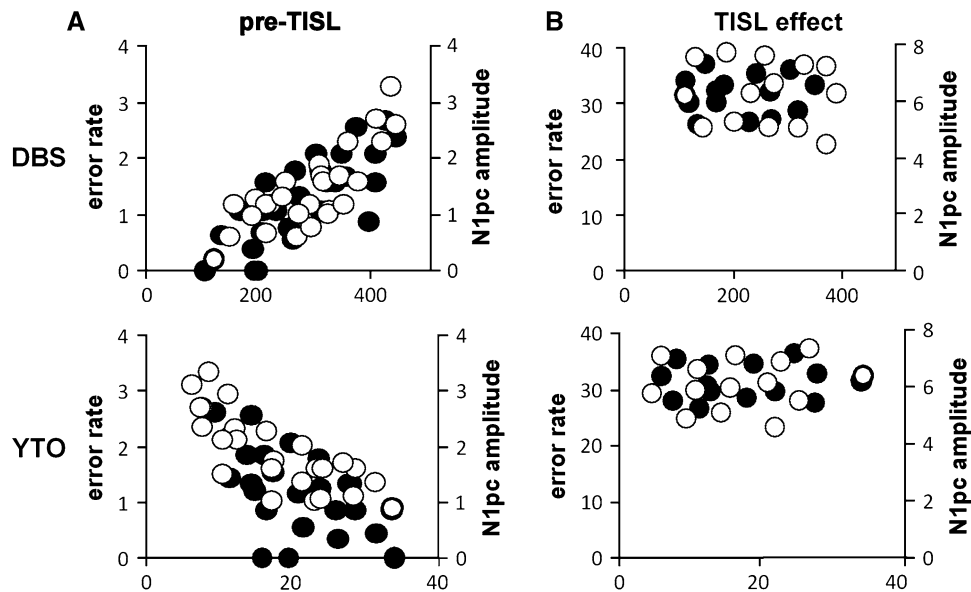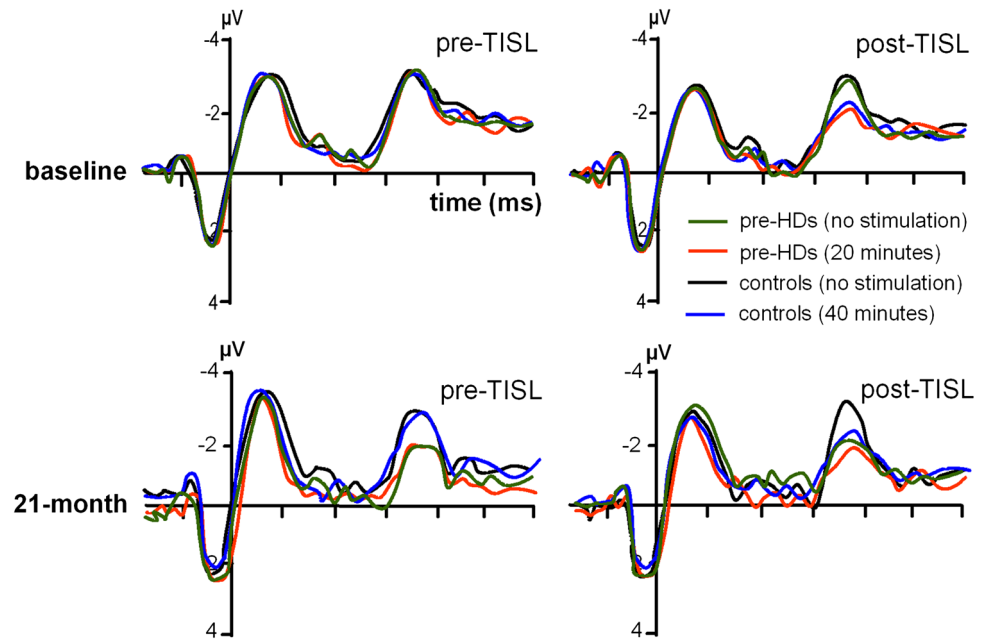

Fig. 5 Scatterplots of the regression analyses. **a** Scatterplots denoting the correlation between declines in pre-TISL performance and DBS (*top*), as well as the estimated years to onset (YTO) (*bottom*). The left ordinate in the plots (referring to *black dots*) denotes declines in behavioral performance, and the right ordinate denotes changes in N1pc amplitude (referring to *white dots*). **b** Scatterplots denoting the correlation between the effect induced by TISL and DBS (*top*), as well as the estimated YTO (*bottom*). The left ordinate in the plots (*black dots*) denotes behavioral effects, and the right ordinate denotes N1pc amplitude effects (*white dots*)

"pre-stimulation/post-stimulation × longitudinal time-point × group" ($F < 0.5$; $p > 0.4$). There was only an interaction of "pre-stimulation/post-stimulation × group" ($F(3,52) = 5.99$; $p = 0.0001$) showing that the N2pc is lower in groups after EBL compared to groups where no EBL was induced ($p = 0.005$). There was also no interaction effect of "longitudinal time-point × group" ($F < 0.2$; $p > 0.7$), showing that attentional re-allocation processes were not affected by pre-manifest HD progression.

The fronto-central N2 is shown in Fig. 4.

An analysis of the fronto-central N2 in the mixed effects ANOVA revealed an interaction of "longitudinal time-point × group" ($F(3,52) = 7.87$; $p = 0.0001$; $\eta^2 = 0.25$), showing that the N2 became smaller in pre-HD across longitudinal time-points ($p = 0.007$), while in controls, no effect of longitudinal time-point was evident ($p > 0.3$). Moreover, there was an interaction of "pre-stimulation/ post-stimulation × group" ($F(3,52) = 6.23$; $p = 0.0001$),

showing that the N2 became smaller after EBL, compared to groups receiving no EBL between the test sessions ($p = 0.01$). This effect has been shown previously (Beste et al. 2012), as it has been suggested that the reduction of the fronto-central N2, and hence a reduction in perceptual conflict, is a consequence of EBL effects on the N1pc (i.e., after EBL, attention is initially directed to the target and is not distracted by the orientation change in the LOB condition). There was no interaction of "pre-stimulation/post-stimulation × longitudinal time-point × group" ($F < 0.2$; $p > 0.7$), suggesting that the effect of EBL was similarly large for the pre-HD and control groups across longitudinal time-points.

Correlational analyses

Correlational analyses were performed using the years until the estimated age of onset (YTO), as calculated by Langbehn et al. (2004), and the DBS (Tabrizi et al. 2009) (see "Methods" section). The scatterplots are shown in Fig. 5.

Behavioral and N1pc data showed that pre-TISL attentional selection declines were stronger in pre-HDs closer to the estimated age of onset e(AO) (all $r > 0.6$; $R^2 > 0.36$; $p < 0.001$), and a higher DBS was related to stronger declines (Fig. 5a) (all $r > -0.5$; $R^2 > 0.25$; $p < 0.004$). Such a correlation was also evident in the baseline data (cf. Beste et al. 2012). In contrast, across longitudinal time-points, these parameters were not related to changes in the degree of TISL effects at the behavioral and neurophysiological level (all $r < 0.2$; $p > 0.2$) (Fig. 5b).

Discussion

In the current study, we investigated pre-manifest HD as a possible human disease model related to excitotoxic neurodegeneration and investigate whether such processes are related to divergent effects on cognitive functions. To this end we analyzed the effects of pre-manifest HD disease progression on neural plasticity effects on attentional selection processes.

The results show that, prior to the induction of TISL, attentional selection processes show a longitudinal decline in attentional selection functions across a 21-month longitudinal period in pre-manifest HD, as shown in the decreased ability to detect the target stimulus (luminance change) in the attentional demanding condition. This was also reflected by the neurophysiological (N1pc) data. The N1pc became increasingly positive across the 21-month longitudinal period. This suggests that attentional selection becomes increasingly distractible, throughout pre-manifest disease progression. This finding is in line with that of other studies on attentional selection processes in HD (e.g.,

Georgiou-Karistianis et al. 2002, 2012; Farrow et al. 2006; Finke et al. 2006).

However, the data on the TISL effects suggest that neural plasticity processes became more efficient over the 21-month longitudinal period. The degree of learning induced by TISL was stronger for the 21-month endpoint compared to the baseline measurement. This effect was evident in the behavioral and neurophysiological data (N1pc). After the induction of TISL, the N1pc turned negative, suggesting that attention becomes no longer distracted by concomitant orientation change (Beste et al. 2012). This effect was even stronger for the 21-month endpoint. However, this effect is not only due to the declines in attentional selection performance prior to the induction of TISL. The behavioral data show that the performance level after TISL was larger for the 21-month endpoint compared to baseline. Similarly, the N1pc amplitude was more negative after TISL in pre-HDs for the 21-month endpoint compared to baseline. This shows that there is an absolute gain in plasticity effects, and not just a relative gain in neural plasticity that is due to declines in attentional selection prior to the induction of TISL. Hence, the data account for divergent developmental trajectories in effects of neurodegenerative processes related to different cognitive processes, since the examined pre-TISL attentional selection processes showed declines across longitudinal time-points. As expected, the ambivalence of effects emerges on different time scales: In the long term (i.e., across longitudinal time-points), attentional selection processes decline, possibly because excitotoxicity weakens structural neuronal integrity. Over much shorter time scales (i.e., TISL effects), increased glutamatergic neural transmission can augment neural plasticity processes, despite weakened structural neuronal integrity. The results moreover show that the divergence of effects are restricted to a subset of attentional selection functions, since for the N2pc and the fronto-central N2 there was no evidence for a differential modulation of task performance. This suggests that attentional re-allocation processes and conflict-monitoring processes do not show divergent developmental trajectories. The fronto-central N2 only revealed declines in pre-HD subjects across longitudinal time-points, which likely reflects neurodegenerative processes observed in several conditions affecting fronto-striatal circuits (Willemssen et al. 2011; Verleger et al. 2010; Nguyen et al. 2010). This is in line with findings showing declines in the fronto-central N2 in pre-manifest HD and manifest HD (Beste et al. 2008b, 2012). Divergent developmental trajectories are hence restricted to a subset of cognitive processes.

One can only infer on the neurobiological processes leading to the effects observed. However, since HD is associated with excitotoxic neurodegeneration (e.g.,

Milnerwood et al. 2010; Okamoto et al. 2009) and neural plasticity effects are well-known to depend on glutamatergic neural transmission the results observed are likely to reflect ambivalent effects attributable to the "NMDA receptor paradox" (Hardingham and Bading 2010). The results suggest that this ambivalence increases throughout disease progression. However, while pathogenic mechanisms in HD are known to primarily affect fronto-striatal loops, previous studies have shown that striate and extrastriate visual areas (BA17-19) show strong degenerative changes in HD (Rosas et al. 2005, 2008), that may emerge due to glutamatergic alterations being profound in visual cortices (Storey et al. 1992: for discussion see: Rosas et al. 2008). Therefore attentional selection processes and effects of neural plasticity processes likely occurring in these areas (e.g., Beste et al. 2012) are modulated in pre-manifest HD.

It may be speculated that these paradoxical effects are mediated via distinct neurobiological processes. To substantiate the above hypotheses about the neural mechanisms the results of the regression analysis are important, which revealed a dissociated pattern: There was a strong linear correlation between declines in attentional selection processes (i.e., prior to TISL) at the behavioral and neurophysiological level when pre-HDs were closer to the eAO, and revealed a higher DBS. For the degree of learning, no such correlations were obtained. Phasic effects mediating neural plasticity have been related to synaptic NMDA receptors (Hardingham and Bading 2010). In contrast, chronic glutamatergic agonism mediating death-promoting effects is achieved via extrasynaptic NMDA receptors (Hardingham and Bading 2010; Xu et al. 2009). These extrasynaptic receptors, but not the synaptic NMDA receptors, have been shown to contribute to phenotype onset in HD, as determined by the underlying genetic mutation (Milnerwood et al. 2010; Okamoto et al. 2009). This dissociated pattern regarding correlations between the degree of plasticity effects and the e(AO) may hence be interpreted as a hint that different NMDA receptor subtypes may underlie the divergent effects of pre-manifest HD disease progression on neural plasticity processes and attentional selection processes. However, it has to be noted that, for the baseline data, a correlation between the degree of learning and the eAO, as well as the DBS was evident (cf. Beste et al. 2012). However, at a single time-point, the degree of plasticity is confounded with the degree of neurodegeneration, but this was not the case in the current longitudinal data.

In summary, the data show that pre-manifest HD disease progression, associated with excitotoxic pathophysiological mechanisms, has ambivalent effects on cognitive functions. Our results show that circumscribed enhancements of specific cognitive functions (i.e., neural plasticity processes) are as much a result of the developmental process of neurodegeneration as the well-known detrimental effects. The results also show that there is an absolute gain in plasticity effects and not just a relative gain in neural plasticity that is due to declines in attentional selection prior to the induction of plasticity. The data indicate that neurodegeneration in HD seems to induce divergent developmental trajectories in cognitive functions related to attentional selection and neural plasticity. These effects may be attributable to known divergent effects of excitotoxicity.

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