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Response inhibition subprocesses and dopaminergic pathways: Basal ganglia disease effects

Christian Beste[a,b,*], Rita Willemssen[b], Carsten Saft[c], Michael Falkenstein[b]

[a] Institute for Cognitive Neuroscience, Biopsychology, Ruhr-University of Bochum, Universitätsstraße 150, D-44780 Bochum, Germany
[b] IfADo - Leibniz Research Centre for Working Environment and Human Factors, Dortmund, Germany
[c] Department of Neurology, Ruhr-University of Bochum, Germany

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ABSTRACT

Response inhibition is a component of executive functions, which can be divided into distinct subprocesses by means of event-related potentials (ERPs). These subprocesses are (pre)-motor inhibition and inhibition monitoring, which are probably reflected by the Nogo-N2 and Nogo-P3, respectively. Here we ask, if these subprocesses may depend on distinct basal ganglia subsystems. We examined response inhibition processes in an extended sample of young and elderly subjects, patients with Parkinson's disease (PD) and Huntington' disease (HD). This combination of groups also allow us to study whether, and to what degree, pathological basal ganglia changes and healthy aging have similar and/or different effects on these processes. We show that subprocesses of response inhibition are differentially modulated by distinct basal ganglia circuits. Processes related to (pre)-motor inhibition appear to be modulated by the nigrostriatal system, and are sensitive to aging and age-related basal ganglia diseases (i.e. PD). Parkinson's disease induces additive effects of aging and pathology. In contrast, inhibition monitoring is most likely modulated by the mesocortico-limbic dopamine system. These processes are equally affected in healthy aging and both basal ganglia diseases (i.e. PD, HD).

1. Introduction

Response inhibition, a component of executive functions (Mostofsky & Simmonds, 2008) depends on basal ganglia–prefrontal interactions (Chudasama & Robbins, 2006). It has been shown that aging affects these interactions (e.g. Buckner, 2004) and also patients suffering from basal ganglia disorders, like Parkinson's (PD) or Huntington's disease (HD) show severe dysfunctions in cognitive processes mediated by these circuits (e.g. Caballol, Marti, & Tolosa, 2007; Salmon & Filoteo, 2007).

Response inhibition subprocesses can be examined in a Go/Nogo-task, in which subjects are asked to respond to one stimulus (Go) and to refrain from responding to the other stimulus (Nogo), by means of event-related potentials (ERPs). Here, Nogo-stimuli elicit a fronto-central negative-positive complex (Falkenstein, Hoormann, & Hohnsbein, 1999) that has been labeled as Nogo-N2 and Nogo-P3 (e.g. Bokura, Yamaguchi, & Kobayashi, 2001; Falkenstein et al., 1999). It has been suggested that the Nogo-N2 (Falkenstein et al., 1999) reflects inhibition or revision of a motor plan/program before the actual motor process. The Nogo-N2 might either be a specific component, which is only present when control is needed, or rather a special case of a more general process. Such a process, which would be also reflected in the N2b, might be response selection (Beste et al., 2008a,b; Gajewski, Stoerig, & Falkenstein, 2008; Willemssen, Falkenstein, Schwarz, Müller, & Beste, 2009), which is intensified in critical situations, such as incompatible or Nogo-trials. Converging evidence argues for the former view, i.e. that the N2 contains a component which is specific for inhibition or control (Falkenstein, Hoormann, & Hohnsbein, 2002).

The Nogo-P3 is related to motor inhibition (e.g. Smith, Johnstone, & Barry, 2006; Smith, Johnstone, & Barry, 2008; Zordan, Sarlo, & Stablum, 2008). Because of its long latency, the Nogo-P3 has alternatively been suggested to reflect the monitoring of the outcome of inhibition (Schmajuk, Liotti, Busse, & Woldorff, 2006) rather than motor inhibition itself. Such monitoring functions are associated with the anterior cingulate cortex (ACC), which has been suggested to generate the Nogo-P3 (Beste et al., 2008a,b; Fallgatter et al., 2004; Schmajuk et al., 2006). This underlines that the Nogo-P3 may reflect an evaluation processes. The Nogo-P3 is certainly different from the usual parietal P3b, which occurs after targets, also due to its different scalp topography. It is also not likely to be a P3a, which reflects orienting to rare or novel stimuli (which also has a frontal or fronto-central topography) since the Nogo-P3 was

* Corresponding author at: Institute for Cognitive Neuroscience, Biopsychology, Ruhr-University Bochum, Universitätsstraße 150, D-44780 Bochum, Germany. Tel.: +49 234 322 4323; fax: +49 234 321 4377.
E-mail address: christian.beste@rub.de (C. Beste).

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much smaller or nor present at all in Go trials (see also Falkenstein et al., 2002), which had the same probability.

Several existing studies in literature suggest that Parkinson's disease patients show impairments in inhibitory control. Bokura et al. (2005) found a reduction and delay of Nogo-N2 and Nogo-P3 in PD-patients and hence claimed that patients with PD show impairments in inhibitory functioning. Falkenstein, Willemssen, Hohnsbein, and Hielscher (2006) found that PD-patients are less likely to respond to irrelevant stimuli. This suggests an enhancement of inhibitory control in PD. Recently, our group accounted for impairments of inhibitory control in Parkinson's disease in experiments varying stimulus–response compatibility (Beste, Dziobek, Hielscher, Willemssen, & Falkenstein, 2009). Concerning another basal ganglia disorder, i.e. Huntington's disease (HD), a response inhibition deficit is also reported (Aron et al., 2003), and further validated using ERPs (Beste et al., 2008a,b).

In the current study we ask whether these subprocesses underlying response inhibition are mediated by different basal ganglia subsystems. This question can only be answered, if basal ganglia disease groups are compared that show overlaps as well as dissociations of involved basal ganglia circuits and/or brain regions. Doing so, we compare response inhibition in PD, HD and aging, since these groups show different as well as common pathophysiologies in the midbrain dopaminergic system (DA-system). While motor symptoms in PD are related to the degeneration of the nigrostriatal pathway (e.g. Gale, Amirnovin, Williams, Flaherty, & Eskandar, 2008), several cognitive deficits in PD, especially in executive functions, are due to dysfunctions in mesocortico-limbic pathways (e.g. Ito et al., 2002; Schott et al., 2007), even though other brain areas as well as neurotransmitter systems are impaired in PD (e.g. Ahlskog, 2007). Regarding neocortical brain areas, regions affected in PD largely overlap with regions affected in HD. Huntington's disease (HD) is accompanied by diffuse neurodegeneration affecting several regions across the whole brain (Rosas, Feigin, & Hersch, 2004) and several neurotransmitter systems (Yohrling & Cha, 2002). Dysfunction in striatal medium spiny neurons (MSNs) and mesocortico-limbic pathways (Mitchell, Cooper, & Griffiths, 1999) play a major role.

Even though there is a large overlap of neocortical pathology and neurotransmitter systems in PD and HD, pathologies seem to differ regarding the involvement of the nigrostriatal and the mesocortico-limbic dopamine system. This differential involvement of distinct basal ganglia pathways offers an opportunity to dissociate the contribution of these pathways with respect to response inhibition processes. A function that is specifically involved in one disease characterized by changes in one of these pathways (e.g. nigrostriatal system in PD), but not in the other disease (i.e. HD) should be attributable to these neuronal changes; and vice versa. If a functional subdivision is comparably modulated across diseases, a cognitive function should be comparably modulated across diseases. Upon this logic ERPs reflecting different response inhibition subprocesses can be evaluated with respect to the importance of specific basal ganglia pathways. Based upon this logic, the following specific predictions may be proposed:

- The initiation of motor programs and the execution of movements are closely related to the nigrostriatal system, as evidence by motor symptoms in Parkinson's disease that are attributed to a nigrostriatal dysfunctions (Gale et al., 2008; Nieoullon, 2002). Due to the importance of this system, especially for motor functions, also (pre)-motor processes of inhibition (Nogo-N2) predominantly rely on the nigrostriatal pathway, PD and elderly (e.g. Collier et al., 2007; Gale et al., 2008), but not HDs should reveal alterations compared to young controls. This is because the nigrostriatal system is not dysfunctional in young controls and also not or less dysfunctional in HD.
- If outcome monitoring of inhibition (Nogo-P3) is predominantly related to the mesocortico-limbic system, this function should be equally affected in elderly, HDs and PDs. This is since (i) the mesocortico-limbic system, subserving medial prefrontal areas that mediate monitoring functions (Beste et al., 2008a,b; Rushworth & Taylor, 2007; Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006) is affected in elderly, HDs and PDs, and (ii) since effects of PD, HD and aging has been shown to similarly modulate a cognitive function depending on the mesocortico-limbic system (Wild-Wall, Willemssen, Falkenstein, & Beste, 2008).

In summary, we investigate if subprocesses of response inhibition may differentially be modulated by distinct basal ganglia circuits and between HD, PD and aging. Processes associated with (pre)-motor inhibition should be modulated by the nigrostriatal system, while monitoring processes should be associated with the mesocortico-limbic DA-system.

2. Materials and methods

2.1. Participants

A group of 14 right-handed, un-medicated HD-patients defined by a positive gene test and manifest clinical symptoms from 21 to 57 years of age ($M = 36.5$; S.D. = 10.2) were recruited. Additionally 14 right-handed presymptomatic gene mutation carriers (pHD) from 22 to 51 years of age ($M = 35.9$; S.D. = 10.03) were recruited. The UHDRS motor scores from these groups (see Table 1) clearly underline that the pHD-group was without manifest symptoms (i.e. UHDRS motor score = 0).

Besides the Huntington groups, a group with medicated patients suffering from Parkinson's disease (right-handed) (PD) ($N = 18$) from 40 to 75 years of age ($M = 60.5$; S.D. = 11.6) was recruited. This group was tested after overnight withdrawal (12–14 h) of medication (off-medication). All these clinical groups were complemented by two healthy right-handed control groups, one young group ($N = 13$) from 22 to 51 years of age ($M = 36.1$; S.D. = 8.5), which is comparable to the HD-groups and an elderly group ($N = 18$) from 41 to 75 years of age ($M = 60.4$; S.D. = 11.6), which also served as control group for the PD-patients. More detailed demographical data is given in Table 1. Dose and type of medication in the PD-group are given in Table 2.

All 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.

2.2. Stimuli and procedure

To measure inhibitory processes, we used a Go/Nogo-task. One out of two words was presented on a PC-monitor: "press" (Go-stimulus) and "stop" (Nogo-stimulus). The stimuli were displayed for 300 ms. The response-stimulus interval was fixed at 1600 ms. In trials with response times exceeding the deadline of 1200 ms a feedback stimulus (1000 Hz, 60 dB SPL) was given. This stimulus had to be avoided by the subjects. Two blocks of 60 stimuli each were presented in this task. Go- and Nogo-stimuli were presented equally frequent. The subjects had to react with the thumb to "Go-stimuli" and to refrain from responding on "Nogo-stimuli". A response was given by pressing a button at the top of a joystick-like vertical bar. The response button had to be operated either with the right or left hand thumb. The left or right response hand use was counterbalanced across subjects.

2.3. Data processing and analysis

During the task the EEG was recorded from 24 Ag–AgCl electrodes (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, FCz, FC3, FC4, FC5, FC6, C3, C4, C7, C8, Pz, P3, P4, P7, P8, Oz, O1, O2, left mastoid – M1, right mastoid – M2) against a reference electrode located at Cz. Additionally, eye movements were monitored and recorded by means of two lateral and four vertical EOG electrodes. The sampling rate of all recordings was 500 Hz, applying a filter bandwidth 0–80 Hz to the EEG. Electrode impedances were kept below 5 kΩ. EEG was filtered off-line from 0.5 to 16 Hz and re-referenced to linked mastoids. Artifact rejection procedures were applied twice: automatically, with an amplitude threshold of ±80 μV, and visually by rejecting all trials contaminated by technical artifacts. Due to artefact elimination approximately 10% percent of trials were discarded. This was the case for Go- and Nogo-trials. Horizontal and vertical eye movements contained in the accepted trials were corrected by means of a linear regression method for EOG correction (Gratton, Coles, & Donchin, 1983). Results of the ocular correction procedure were visually inspected to be sure that the regression method did not distort frontal channels. Subsequent to averaging N2 and

Table 1
Descriptive data for the different groups of ages, sex, general level of intelligence (MWT-B), depression (BDI), Mini-Mental Status Examination (MMSE), Unified Parkinson's Disease Rating Scale (UPDRS)/Unified Huntington's Disease Rating Scale (UHDRS motor scores), CAG-repeat size (CAG), estimated age of onset (eAO) and the age of onset (AO). The latter three are only given for the appropriate HD-group.

	YOUNG		OLD		PD		pHD		HD	
	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)	Range
Age	36.10 (8.50)	22-51	60.4 (11.6)	41–75	60.5 (11.6)	40–75	35.91 (10.03)	22–51	36.50 (10.20)	21–57
Sex	6 females/7 males		6 females/12 males		6 females/12 males		7 females/7 males		7 females/7 males	
MWT-B	113 (9.11)	99–126	121.0 (13.5)	97–143	115.3 (12.4)	94–136	112 (10.13)	95–125	110 (12.15)	98–120
Beck Depression Inventory (BDI)	3.10 (3.12)	0–11	4.1 (3.6)	0–10	5.6 (5.2)	0–19	5.74 (4.30)	0–12	5.90 (4.06)	0–12
Mini-Mental State Examination (MMSE)	NA	NA	28.7 (1.1)	26–30	28.7 (1.3)	26–30	29.50 (0.51)	(29–30)	28.10 (2.12)	24–30
Clinical scores										
UPDRS/UHDRS	NA	NA	NA	NA	14.6 (9.1)	2–30	0 (0)	0	25 (11.12)	9–42
CAG	NA	NA	NA	NA	NA	NA	42.81 (1.77)	39–46	46.10 (5.52)	40–55
eAO	NA	NA	NA	NA	NA	NA	45.54 (4.87)	37.5–53.2	NA	NA
AO	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 2
Anti-parkinsonian medication for medicated PD per day in milligram (mg).

Patient	Medication (dose per day in mg)	Patient	Medication (dose per day in mg)
1	Pr 0.8; A 200	10	L 100; Rop 10
2	L 437.5; C 2	11	Rot 16
3	L 187.5; Rop 6; A 300	12	Ra 1
4	Rop 12	13	Rot 8
5	L 100; Rop 4.5; A 300	14	Pr 0.35
6	Ra 1; Pr 1.05	15	Ra 1
7	S 5; C 1	16	Ra 1
8	S 5; Rop 12	17	Ra 1; Rot 4
9	L 125	18	Ra 1; Rot 8

A = amantadin, C = cabergolin, L = L-dopa, Pr = pramipexol, Ra = rasagilin, Rop = ropinirol, Rot = rotigotin, S = seregilin.

P3 amplitudes in Go- and Nogo-trials were evaluated using the correct trials only. After digital low-pass filtering the amplitudes were measured relative to a 200 ms pre-stimulus baseline.

The N2 was defined as the most negative peak occurring 200 till 300 ms after stimulus onset and was measured relative to baseline. The P3 was defined as the most positive peak occurring 300–500 ms after stimulus onset and was measured relative to baseline. Amplitudes and latencies were measured for each group separately. This scoring method is comparable to that other studies. The neurophysiological data of the N2 and P3 were analyzed in two separate repeated measures ANOVAs. The N2 data were analyzed using the factors "electrode" (Fz, FCz, Cz) and "Go/Nogo" as within-subject factors and "group" as between subject factor. For the P3-data the electrodes FCz and Pz were analyzed with the same design. Greenhouse–Geisser corrections were applied when appropriate. For post-hoc tests an Scheffe-contrast procedure was applied. In cases, where univariate or a repeated measures ANOVAs were necessary as post-hoc tests to brake down interaction effects, the level of significance for each test was subsequently adjusted to the number of tests applied, i.e. a Bonferroni-correction was conducted.

3. Results

3.1. Behavioral data

For the response times (RTs) the mean and standard error of the mean (S.E.M.) are given. To assess group differences in performance RTs and the number of false alarms in Nogo-trials were subjected to separate univariate ANOVAs with the between subject factor group. The response times (RTs) are given in Fig. 1A, the absolute frequency of false alarms are given in Fig. 1B.

Response times (RTs) differed between the groups ($F(4,72) = 4.8$; $p < .001$). Scheffe contrasts revealed that all disease groups and the elderly controls showed slower RTs, compared to healthy young controls ($p < .05$). The disease groups and elderly controls did not

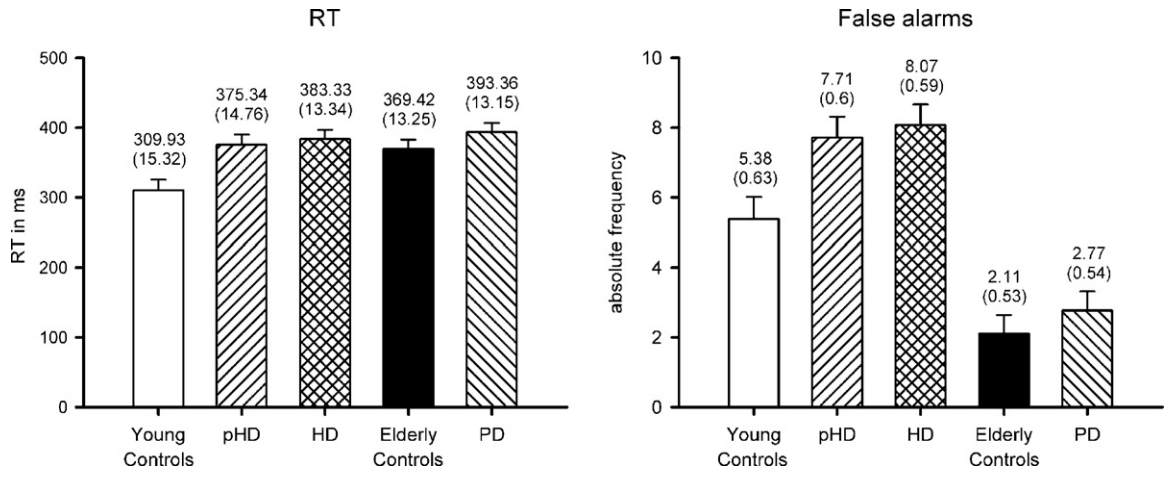

Fig. 1. (A) Mean response times (RTs) (in ms) (±standard error of the mean, S.E.M.) on Go-trials separated for the groups. (B) Absolute frequency of false alarms on Nogo-trials (±standard error of the mean, S.E.M.) separated for the groups.

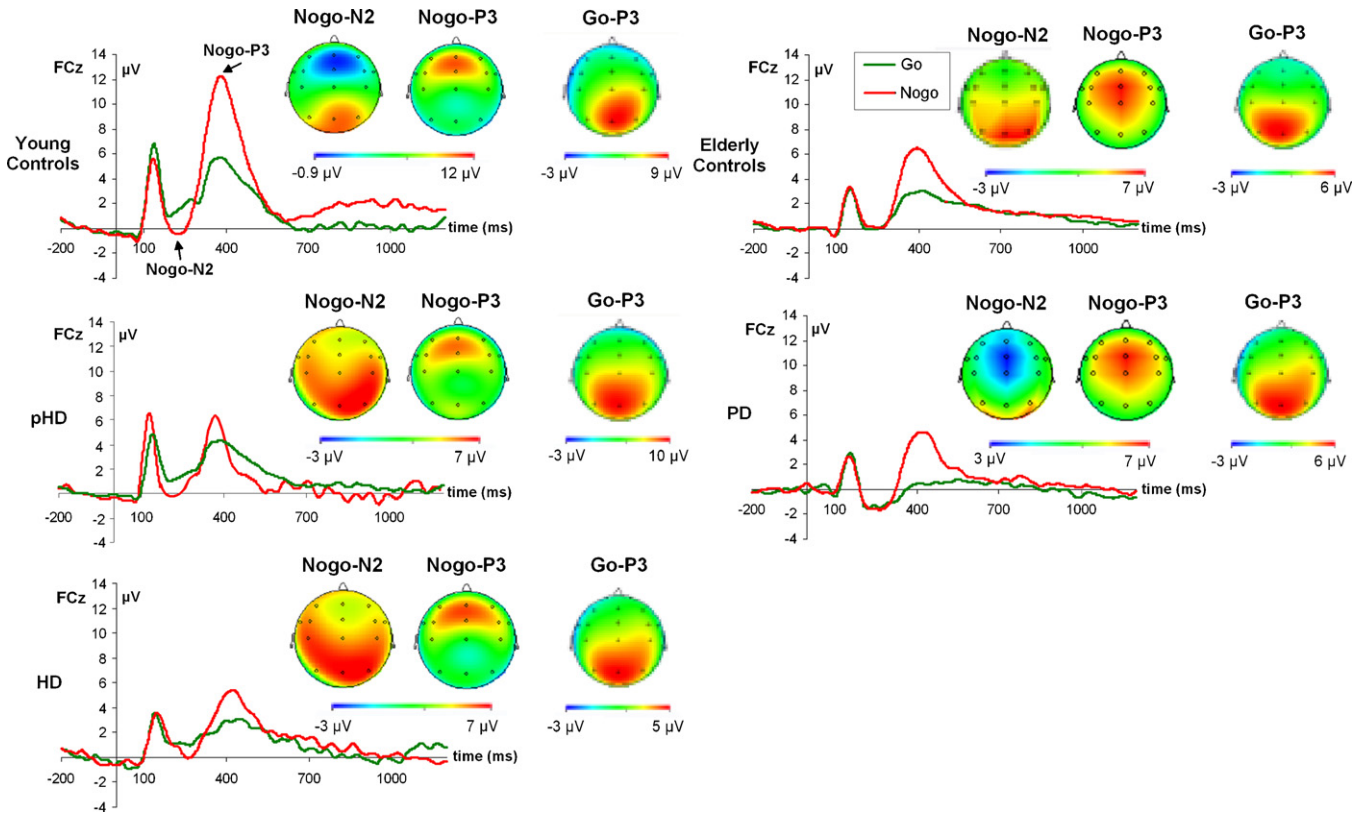

Fig. 2. Stimulus-locked event-related potentials at electrode FCz (ERPs) on Go-trial (green line) and Nogo-trial (red line), combined with the scalp topography of the Nogo-components (Nogo-N2, Nogo-P3) and the P3 on Go-trials, separated for each group. Time point 0 denotes the point of stimulus presentation. Amplitudes are given in μV. Positivity is plotted upward. Note: The scaling of the scalp topography plots in the young control group is different from the other groups. Also the scaling of the Go-P3 topography is different. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

differ from each other ($p > .9$). Also the frequency of false alarms differed between the groups ($F(4,72) = 22.9$; $p < .001$). An Scheffe-contrast procedure was applied to compare the groups with each other. HD (8.1 ± 0.6) and pHD-patients (7.7 ± 0.6) showed most false alarms, not differing from each other ($p > .9$). In both of these groups, the number of false alarms was significantly higher than in young controls (5.4 ± 0.6) ($p < .05$). The lowest false alarm rates were seen in the elderly controls (2.1 ± 0.5) and the PD-group (2.7 ± 0.5), not differing from each other ($p > .9$). Both of these groups showed fewer false alarms than all other groups ($p < .04$).

3.2. Neurophysiological data

The grand means of the waveforms are given in Fig. 2.

3.3. N2-effects

The N2 differed between the electrode sites, being more negative at electrode Fz (-0.81 ± 0.2), compared to Cz (-0.23 ± 0.1) ($p < .05$). No difference was seen contrasting Fz against FCz (-0.6 ± 0.2) ($F(2,144) = 4.3$; $p = .015$). The N2 was also larger on Nogo-trials (-0.9 ± 0.1) compared to Go-trials (-0.2 ± 0.2) ($F(1,72) = 26.1$; $p < .001$) and also differed between groups ($F(4,72) = 13.0$; $p < .001$). Group differences in the N2 are given in Fig. 3A. To compare the N2 between the groups an Scheffe-contrast procedure was applied.

More negative N2-amplitudes in the PD-group were evident, compared to all other groups ($p < .005$), which did not differ from each other ($p > .25$). This effect was different for Go- and Nogo-trials, as revealed by the interaction "Go/Nogo × group" ($F(4,72) = 6.7$; $p < .001$). Fig. 3C depicts amplitudes on Go- and Nogo-trials for each group. Comparing amplitudes on Go- and Nogo-trials within each group it is shown that amplitudes did not differ in PD-patients and elderly controls (all F's < 0.8; $p > .372$), while there were differences in all other groups (all F's > 8.5; $p < .013$). Here amplitudes were more negative on Nogo-trials compared to Go-trials. The Go/Nogo effect was also different for the electrode sites (electrode × Go/Nogo: $F(2,144) = 7.3$; $p < .001$).

Using repeated measures ANOVAs as post-hoc tests a difference in amplitudes between Go- and Nogo-trials has been observed at electrode Fz (Go: -0.5 ± 0.2; Nogo: -1.3 ± 0.2) and FCz (Go: -0.3 ± 0.3; Nogo: -1.2 ± 0.2) (F's > 14.5; $p < .001$), but not at Cz (Go: -0.2 ± 0.2; Nogo: -0.4 ± 0.1) ($p > .2$). There were no other interaction effects.

The latencies differed between electrodes Fz (242 ± 2) and Cz (235 ± 2) ($p = .022$), but there was no difference to FCz (239 ± 2) ($p > .3$) ($F(2,8) = 5.3$; $p = .006$).

3.4. P3-effects

The P3 was larger for Nogo (6.6 ± 0.2), than for the Go-trials (6.1 ± 0.1) ($F(1,72) = 8.3$; $p = .005$) and also differed between groups ($F(4,72) = 22.5$; $p < .001$) as can be seen in Fig. 3B. An Scheffe-contrast procedure revealed that PDs showed the lowest P3, differing from all other groups ($p < .006$) except the elderly control group ($p > .7$). The latter only differed from young controls and pHDs ($p < .001$). PHDs differed from PDs and elderly controls ($p < .001$). The young controls showed higher amplitudes than all other groups ($p < .011$), except the pHD-group ($p > .7$).

However, the group effect was different for the electrodes and Go/Nogo (electrode × Go/Nogo × group: $F(4,72) = 5.9$; $p < .001$). This interaction was subsequently broken down using repeated mea-

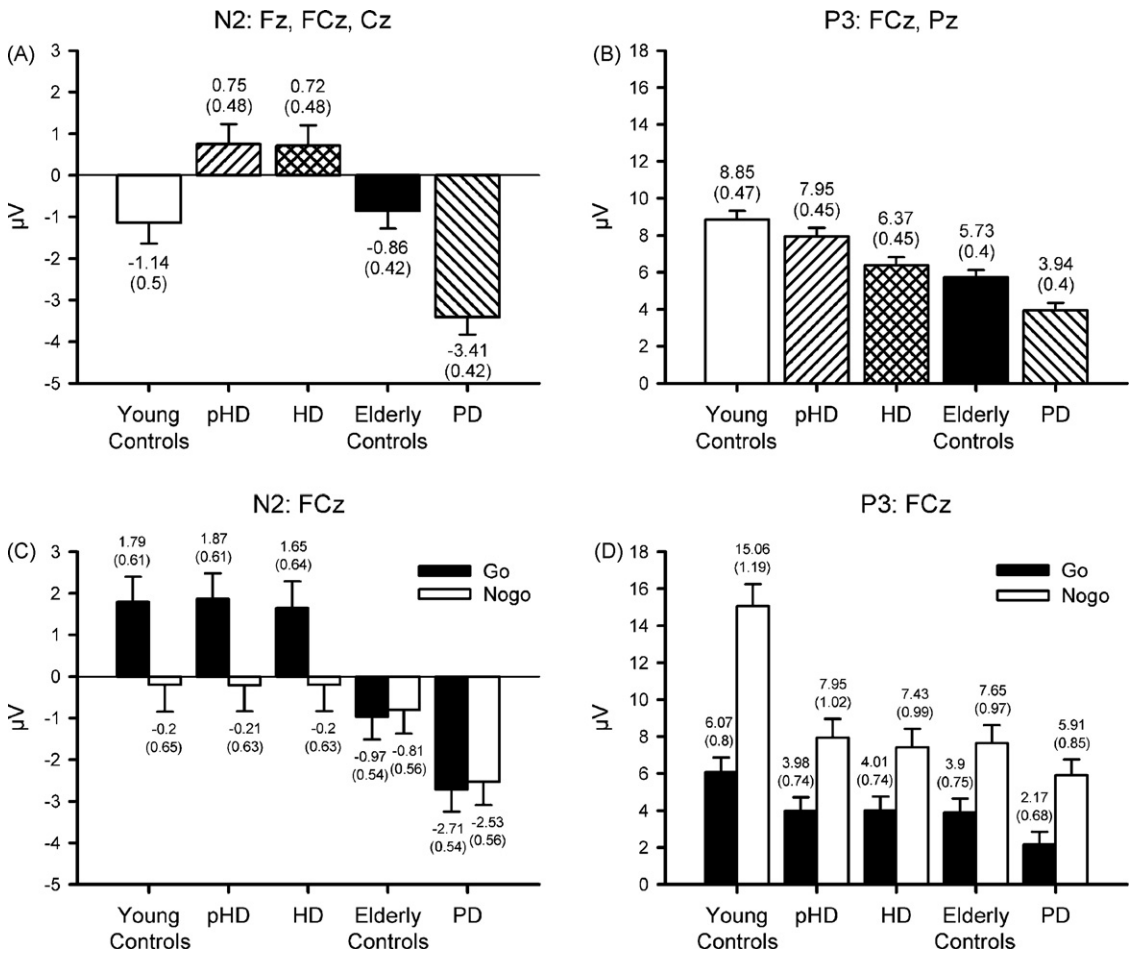

Fig. 3. The groups are denoted as YC = young control, HD = symptomatic HD, pHD = presymptomatic HD, PD = Parkinson's disease, EC = elderly controls. (A) Mean overall N2 amplitude across electrodes Fz, FCZ and Cz, collapsed over Go- and Nogo-trials, separated for each groups (±standard error of the mean, S.E.M.). (B) Mean overall P3 amplitude across electrodes FCz and Pz, collapsed over Go- and Nogo-trials, separated for each groups (±standard error of the mean, S.E.M.). (C) Mean amplitudes of the N2-component at electrode FCz specified for Go- and Nogo-trials, separated for each group (±standard error of the mean, S.E.M.). As can be seen, the N2 does not differ between the trial types in ECs and PDs, whereas the other groups showed differences in the modulation. (D) Mean amplitudes of the P3-component at electrode FCz specified for Go- and Nogo-trials, separated for each group. As can be seen, the modulation between the trial types was strongest in YCs and comparably weak in all other groups (HD, pHD, PD, EC).

sures ANOVAs for each electrode separately. Here a significant interaction "Go/Nogo × group" for the electrode FCz ($F(4,72) = 7.8$; $p < .001$), but not for Pz ($F(4,72) = 0.6$; $p > .6$) was obtained. Hence only FCz was analyzed further. Go- and Nogo-amplitudes differed from each other within all groups (all F's > 6.3; $p < .024$), but the absolute difference between Go- and Nogo-amplitudes was highest in the young control group (8.9 ± 0.8) and differed from all other groups ($p < .001$) (see Fig. 3D). This pattern is underlined in the overall analysis on FCz and Pz where a difference in amplitude was only evident in the young controls (Go: 7.5 ± 0.4; Nogo: 10.1 ± 0.7) ($F(1,12) = 22.3$; $p < .001$), but not in the other groups (all F's < 1.7; $p > .2$) (group × Go/Nogo: $F(4,72) = 5.8$; $p < .001$). Amplitudes on Go- and Nogo-trials were also different for the different electrodes (Go/Nogo × electrode: $F(1,72) = 204.7$; $p < .001$). The P3 was larger on Nogo-trials (8.8 ± 0.4), compared to Go-trials (4.6 ± 0.3) ($F(1,72) = 79.95$; $p < .001$) at FCz. This pattern is inverted at electrode Pz, where the P3 was larger on Go-trials (7.5 ± 0.1) than on Nogo-trials (4.4 ± 0.1) ($F(1,72) = 163.2$; $p < .001$). The P3 amplitudes on Go-trials were significantly larger at Pz compared to FCz ($F(1,72) = 58.7$; $p < .001$). There were no other main or interaction effects.

The P3 latency was shorter at electrode Pz (390 ± 3), compared to FCz (407 ± 5) ($F(1,72) = 8.18$; $p = .006$). In accordance to the RT data, which were prolonged in the disease groups and the elderly, compared to young controls, the P3 latency at electrode Pz was also prolonged for the disease groups and the elderly, compared to young controls ($F(4,72) = 3.52$; $p = .001$).

4. Discussion

In the current study we analyzed subprocesses of response inhibition in healthy aging and neurodegenerative basal ganglia disorders, i.e. Huntington's and Parkinson's disease by means of event-related potentials (ERPs). Primarily we examined, if response inhibition subprocesses are mediated by distinct basal ganglia dopaminergic circuits. Besides this, the study also sheds light on the question as to whether disease and age-related basal ganglia changes exert similar effects on response inhibition processes.

The Nogo-N2 and Nogo-P3 amplitudes were differentially affected by age and basal ganglia diseases, i.e. PD and HD, pHD: while the PD-patients and elderly controls showed no difference in the modulation of the N2 between Go- and Nogo-trials, all other groups showed differences between these trial types. The N2 was generally largest in PD-patients. This pattern is mirrored by the behavioral data. In contrast, the P3 revealed differences in the modulation between Go- and Nogo-trials in all groups, but it was largest in the young controls.

4.1. N2-effects

No difference between Go- and Nogo-trials is seen in both elderly controls and patients with PD, whereas all the younger groups, including HD-groups, showed a larger N2 in Nogo- than in Go-trials. Hence the absence of a Go-Nogo difference may primarily be due to the age of the groups. Thus, age-related changes (elderly controls and PDs) are expressed in a lack of difference between Go- and Nogo-trials. Both groups show a deterioration of the nigrostriatal DA-system (e.g. Collier et al., 2007; Gale et al., 2008) and striatal medium spiny neurons (MSNs) (Cass et al., 2007; Chase & Oh, 2000), because the nigrostriatal DA-system affects processing of striatal MSNs (Gurney, Prescott, Wickens, & Redgrave, 2004; Surmeier, Ding, Day, Wang, & Shen, 2007). However, as differences between Go- and Nogo-trials were well present in the HD-groups, which also display severe dysfunction of MSNs (e.g. Cepeda, Wu, Andre, Cummings, & Levine, 2007), MSN dysfunctions alone are not sufficient to change modulations of the N2. It is the additional damage of nigrostriatal pathways (e.g. Collier et al., 2007; Gale et al., 2008), which may cause a lack of modulation between Go- and Nogo-trials, as seen exclusively in PD and healthy elderly in this study. Decreased activity in the nigrostriatal DA-system originating in the pars compacta part of the substantia nigra (SN) has different effects on the direct (normally facilitating movements) and the indirect pathway (normally suppressing movements): the direct pathway becomes less active and the indirect pathway becomes more active. While the pars compacta part of the SN (SNc) mainly projects to the striatum, the SN pars reticulata (SNr) mainly projects to thalamic structures hence affecting neocortical functioning (Chudasama & Robbins, 2006), which is thus the final common pathway of both the direct and the indirect pathways. The SNr-thalamic connections are likely inhibitory in nature (Humphries, Stewart, & Gurney, 2006). An increase of this inhibitory nigral activity, or the indirect pathway (Gale et al., 2008) most probable leads to even more inhibited thalamic circuits. This leads to a predominating inhibitory effect on intended movements (e.g. Gale et al., 2008) and to an equalization of neurophysiological processes, as reflected in the N2, between Go- and Nogo-trials. This is underlined by the low frequency of false alarms observed in PDs and elderly controls. This suggests that dysfunctions of the nigrostriatal system paradoxically seem to have aiding effects on response inhibition. When the nigrostriatal system gets more dysfunctional (i.e. PD), pre-motor inhibitory processes (reflected by the N2) are further strengthened, as can be seen in the more negative N2 in this group. Since PD-patients also display a lack of difference between Go- and Nogo-trials, the pattern seen in PDs is likely to be due to an additive effect of aging and disease-specific pathogenic processes. The absence of a difference between Go- and Nogo-trials is mainly due to an enhanced N2 in Go trials, i.e. enhanced inhibition also in Go trials. This is reflected in an increase in RT and reduction of error rate in the older group. Numerous studies have shown that lesions of nigrostriatal DA-system entail motor disturbances (for review Nieoullon, 2002). As the changes of the N2 are likely due to modulations of the nigrostriatal DA-system the results fit to the hypothesis that the N2 reflects processes related to inhibition on a (pre)-motor level (e.g. Falkenstein et al., 1999) (see also Fig. 4). It cannot be ruled out that the reduced rates of false alarms may rather reflect a strategy than a dysfunction. However, given that, the question appears how the basal ganglia may contribute to it.

Yet, within the discussion of the contribution of nigrostriatal pathways for (pre)-motor inhibition processes also possible influences of the subthalamic nucleus (STN) should be taken into account especially, since the STN is a target region of deep brain stimulation (DBS) to treat PD (for review Benabid, Chabardes, Mitrofanis, & Pollak, 2009). The STN has been shown to exert excitatory influence on the substantia nigra (e.g. Humphries et al., 2006; Temel, Blokland, Steinbusch, & Visser-Vanderwalle, 2005), hence promoting inhibitory influences. Due to (DBS) pathological motor behavior in PD is substantially improved (e.g. Temel et al., 2005). In this respect future studies may examine the effects of DBS on response inhibition.

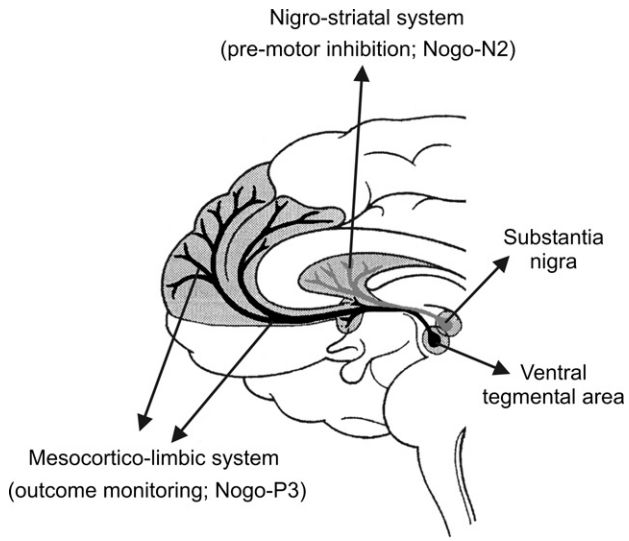

Fig. 4. Schematic illustration of the basal ganglia dopamine system in relation to response inhibition subprocesses. The nigrostriatal DA-system is colored grey, the mesocortico-limbic DA-system is colored black. Processes related to pre-motor inhibition are likely mediated via the nigrostriatal DA-system (reflected by the Nogo-N2); processes related to the evaluation of inhibition (reflected by the Nogo-P3) are likely to be mediated via the mesocortico-limbic DA-system.

The results further suggest an inhibitory deficit in HDs and pHDs, in contrast to PD-patients. This probably arises due to the different modulation of the nigrostriatal system in the mentioned groups. No difference was seen between HDs and young controls, which is in line with other results (Beste et al., 2008a,b). What is hard to explain is the increase in RTs and error rate in the HD-patients compared to the young control group, even though the N2 pattern is similar in these three groups. Hence this impairment of motor performance in HD is not due to alterations of pre-motor cognitive processes (such as pre-motor inhibition as probably reflected in the N2). Rather the impairment is due to very late alterations of response activation in the primary motor cortices, as we have recently shown (Beste et al., 2008a,b).

4.2. P3-effects

While the N2 contrasted older groups (PD, elderly controls) with younger groups (HDs, pHDs and young controls), irrespective of disease, modulations of the Nogo-P3 differentiate between young controls and basal ganglia disorders as well as elderly controls. Modulations between Go- and Nogo-trials were similar for the elderly controls and disease groups (HD, pHD, PD). In recent literature the hypothesis has been raised that the Nogo-P3 is involved in the evaluation of the just preceding response (Roche, Garavan, Foxe, & O'Mara, 2005), which is an inhibitory one in case of a Nogo-trial. Consequently, Schmajuk et al. (2006) stated that the fronto-central P3 reflects the monitoring of the successful outcome of the inhibition process. On Go-trials, the usual parietal P3b is seen, which has recently been associated with the monitoring of proper stimulus–response transformation, which is equivalent with the monitoring of a successful Go response (Verleger, Jaśkowski, & Wascher, 2005). Assuming a source of the Nogo-P3 in the ACC (Beste et al., 2008a,b; Fallgatter et al., 2004; Schmajuk et al., 2006) this monitoring/evaluation account is consistent with a general role of

the ACC in response monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Rushworth & Taylor, 2007; Walton et al., 2006). The Nogo-P3 was much larger in the young compared to all other groups. This result is puzzling, since other studies, including one from our own lab (Falkenstein et al., 2002) showed no significant age-related amplitude difference. However, in that study the RTs were only slightly (24 ms) longer in the elderly compared to the young and the false alarm rate did not differ at all between the groups. In contrast in the present study the RTs were much shorter in the young controls than in all other groups and the false alarm rate was twice as high in the young than in the elderly. Hence the enhanced Nogo-P3 in the young may be due to a stronger monitoring of the inhibition process as a compensatory effort to limit the error rate. Also the present data suggest that the Nogo-P3 is not likely reflecting inhibition per se, given the high error rate despite a large Nogo-P3 in the young. Further studies that modulate error rate via time pressure should be conducted to test this hypothesis. Given this, the current data suggests that these processes generally decline in elderly controls, PDs, HDs and pHDs, in contrast to young controls. Hence, aging effects are not differentiable to effects of basal ganglia disorders with respect to this function. This contrasts with the N2, where age was the main dissociating factor. This result nicely fits to recent results by Wild-Wall et al. (2008), as the mere existence of even subtle dysfunctions of the mesocortico-limbic DA-system is sufficient to alter these monitoring processes (see Fig. 4).

4.3. Remarks

The pattern observed in Parkinson's disease is different to another recent study by our group, where effects of PD were only evident when increasing the demand on response inhibition processes via incompatible S–R relations (Beste et al., 2009). However, most of the differences in the result pattern may stem from the fact that the medication profile between the PD-patient cohorts was different. Related to this also the time span from previous medication was different. Four hours in the Beste et al. (2009) study, 12 till 14 h in the current one. Even though the shorter time span may be assumed to reduce the strength of the effects in the Beste et al. (2009) sample, which was not the case compared to the current sample, it is important to note that disease severity was also different between the studies. The severity of disease (measured via the UPDRS score) was less strong in the current compared to the Beste et al. (2009) sample. This may well affect discrepancies in the effects obtained, all the more as differences in the P3 are stronger in the Beste et al. (2009) sample, compared to the current one. As the strongest between-study differences in ERPs concern the Nogo-P3, medication effects and severity of disease are more likely to affect evaluative processes of response inhibition, rather than (pre-)motor inhibition processes.

It was possible to replicate findings in Huntington's disease (Beste et al., 2008a,b) in the current sample. Both of these, the Beste et al. (2008a,b) and the current sample were un-medicated. This underlines the importance to take differences in the medication profile between studies into account when trying to evaluate results across studies, even when comparable tasks are used.

5. Conclusion

In summary, the results show that subprocesses of response inhibition are differentially modulated by distinct basal ganglia circuits. Processes related to (pre-)motor inhibition seem to be modulated by the nigrostriatal system, while monitoring processes are not affected by this system and may be related to the mesocortico-limbic DA-system (see Fig. 4), even though it cannot be fully excluded that alterations in other neurotransmitter systems may also have an effect.

(Pre)-motor inhibition processes seem to be sensitive to aging, while monitoring processes are sensitive to subtle changes in the mesocortico-limbic DA-system, irrespective of whether these changes are due to aging or to different basal ganglia diseases. The study shows that it may be sensible to compare aging not only to age-related, but also to other basal ganglia disorders in order to gain knowledge about age- and disease-related mechanisms and the effects on cognitive functions. Future studies may have a closer look at frequencies underlying mechanisms of response inhibition (Klimesch, Sauseng, & Hanslmayr, 2007) and should also examine whether the observed effects are specific for the task applied or are generalizable to other Go/Nogo-tasks as well (e.g. stop tasks).

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