ELSEVIER

Neurobiology of Aging 32 (2011) 327–335

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Effects of aging, Parkinson's disease, and dopaminergic medication on response selection and control

Rita Willemssen [a], Michael Falkenstein [a], Michael Schwarz [c], Thomas Müller [b], Christian Beste [a,d,*]

[a] *Leibniz Research Centre for Working Environment and Human Factors, WHO Collaborating Research Centre Dortmund, Germany*
[b] *Department of Neurology, St. Joseph Hospital, Berlin-Weißensee, Germany*
[c] *Department of Neurology, Municipal Hospital Dortmund, Germany*
[d] *Institute for Cognitive Neuroscience, Biopsychology, University of Bochum, Germany*

Received 21 October 2008; received in revised form 31 December 2008; accepted 3 February 2009
Available online 6 March 2009

Abstract

We examined effects of short-term and long-term dopaminergic medication in Parkinson's disease on conflict monitoring or response selection processes. These processes were examined using event-related potentials (ERPs), while subjects performed a stimulus-response (S-R) compatibility task. An extended sample of young and elderly controls, Parkinson's disease patients with a medication history (PDs) and initially diagnosed, drug-naïve de novo PD patients (de novo PDs) were enrolled. Both PD groups were measured twice (on and off-medication or before and 8 weeks after medication onset).

The results show that dopaminergic intervention selectively reduced the pathologically enhanced response selection in compatible S-R relations. This medication effect was already evident after short-term treatment, not differing from long-term treatment and performance in elderly controls. Contrary, age-related attenuations of the N2 in incompatible S-R relations, probably reflecting impaired conflict processing or response control, are unaffected by medication. The results suggest that compatible and incompatible S-R relations demand different neuronal mechanisms within the basal ganglia, as only the former are affected by agonizing the dopaminergic system.
© 2009 Elsevier Inc. All rights reserved.

Keywords: Dopaminergic treatment; Parkinson's disease; Response monitoring; De novo Parkinson's disease; Aging

1. Introduction

The selection and control of responses is a subcomponent of executive functions (Botvinick et al., 2004). These functions can be examined using event-related potentials (ERPs), where they are assumed to be reflected in the N2 component (e.g. Beste et al., 2008; Gajewski et al., 2008; Van Veen and Carter, 2002). In situations without response conflict the N2 is usually small, while it is greatly enhanced when there is conflict between responses that need to be resolved or controlled (e.g. Wild-Wall et al., 2008). The N2 in non conflict trials may exclusively reflect response selection, while in conflict trials an additional component reflecting response, conflict monitoring or control per se, emerges (e.g. Gajewski et al., 2008).

Response selection and control functions may be mediated by the anterior cingulate cortex (ACC) (for review: Botvinick et al., 2004). The ACC is functionally related to the basal ganglia via the mesocortico-limbic system (Chudasama and Robbins, 2006). In the basal ganglia, striatal medium spiny neurons (MSPs) are particularly important for response selection processes (Bar-Gad et al., 2003; Redgrave et al., 1999).

Consequently, it has been shown that dysfunctions in the DA-system reduce the N2, as revealed in elderly people (Ceponiene et al., 2008). Moreover, recent research indicates that response selection and control processes are dysfunctional in various neurodegenerative basal ganglia dis-

* Corresponding author at: IfADo - Leibniz Research Centre for Working Environment and Human Factors, Ardeystr. 67, D-44139 Dortmund, Germany. Tel.: +49 231 1084 212; fax: +49 231 1084 401.
E-mail address: beste@ifado.de (C. Beste).

0197-4580/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2009.02.002

eases like Huntington's disease (e.g. Beste et al., 2008). In Parkinson's disease (PD) the DA-system should be more deteriorated than in normal aging. These dysfunctions may already be evident in initially diagnosed PD (for review: Dauer and Przedborski, 2003). In behavior, deficits in response selection and control could be reflected in enhanced interference effects, as induced by irrelevant stimuli. In PD, several studies found enhanced interference effects (e.g. Praamstra and Plat, 2001; Praamstra et al., 1998; Wylie et al., 2005), but see Falkenstein et al. (2006). However, in these studies patients with a long history of PD were examined, being either under medication or tested after a short time period off-medication.

Basically it is not clear, if response selection processes are already altered in initially diagnosed, drug-naïve de novo PD and how these may differ from healthy age-matched controls. Similarly, it is not clear how de novo PDs differ from PDs with a longer disease history. Furthermore the precise effect of medication is not clear. No comparison between on and off-medicated PD patients was done, yet. Moreover it is not entirely clear, if short-time treatment in initially diagnosed drug-naïve PD (i.e. de novo PD) already affects these functions, and if there is a difference to effects of longer pharmacological intervention.

Comparing a drug-naïve de novo PD group pre and post short time dopaminergic treatment with PD patients having a longer history of dopaminergic treatment on and off-medicated as well as young and elderly controls will allow examining these questions. The comparison against the latter groups allows the examination of disease-specific influences on these processes unbiased of any medication effects. Hence the precise effect of dopaminergic treatment on response selection processes in PD can be examined.

For the N2 it may (i) be hypothesized that the N2 is smaller in healthy elderly subjects, compared to young subjects, but (ii) larger than in PD patients. It may further be hypothesized (iii) that PD patients under stable medication may show similar results to healthy elderly subjects, given that dysfunctions of the DA-system are sufficiently compensated by treatment. Regarding de novo PD before treatment it may be hypothesized (iv) that this group shows more deficient response selection and control processes, compared to healthy controls, due to disease-related influences. Similarly, they may (v) show more deficient response selection and control processes, compared to patients under stable treatment. (vi) If treatment is fully effective even after a short time period in de novo PD patients, these may be similar to elderly controls and patients with longer treatment.

Stimulus-response compatibilities also affect the P3 (e.g. Doucet and Stelmack, 1999; Leuthold and Sommer, 1998). The latency is longer in incompatible than in compatible S-R mappings. Furthermore the P3 is known to be attenuated in elderly people (e.g. Fjell et al., 2007; Kok, 2000) and unspecifically reduced in neurodegenerative diseases (e.g. Antal et al., 1998). However, it is a matter of debate if the P3 depends upon the dopaminergic system. While some studies found evidence for such a modulation (e.g. Berman et al., 2006), some other studies found no dependency (e.g. Beste et al., 2006; Frodl-Bauch et al., 1999). Given that the P3 is not dependent on the dopamine system there should be no effects of disease or treatment and only a dopamine-independent age-effect should be evident.

2. Materials and methods

2.1. Subjects

Four groups were enrolled into the study. A group of 20 medicated patients with idiopathic Parkinson's disease (duration of disease 38.9 (±29.4) months), measured off-medication (>12 after overnight medication withdrawal) and on-medication, was recruited. This group was complemented by 15 initially diagnosed drug-naïve de novo PD patients measured pre and post-medication (2 months after initially medication). PD patients were recruited via the PD outpatient unit of the Department of Neurology, St. Josefs-Hospital, Ruhr-University of Bochum and the Department of Neurology, Klinikum Dortmund. The mean daily dose of anti-parkinsonian medication for medicated PD patients and the initial medication for de novo patients is displayed in Tables 1 and 2.

Additionally a group of 32 healthy elderly subjects and finally a group of 20 younger participants were recruited. Details of the characteristics of all groups are summarized in Table 3. All participants were right-handed.

All subjects were tested with a battery of standard intelligence (MWT-B) routinely used in Germany and neuropsychological tests in a separate session before the main EEG session. As a neuropsychological test of executive functioning the Wisconsin Card Sorting Test (WCST) was used. In order to control for depression, the German version of the Beck depression inventory (BDI) was carried out. The clinical testing with the Unified Parkinson's Disease Rating Scale (UPDRS motor score) was conducted both in the "on (and pre) medication" and the "off (and post) medication" sessions. UPDRS was assessed for each patient by a neurologist, which are outlined in Table 3.

None of the control subjects had any history of either neurological or psychiatric disorders, or was taking any drugs affecting the central nervous system. All participants gave signed informed consent after they were informed about the purpose of the study and the protocol was explained to them. The entire study was approved by the ethics committee of the University of Münster.

2.2. Task

To assess conflict processes we used a modified flanker task (Kopp et al., 1996). The task consisted of vertical arrays of arrowheads or circles. The central part of the stimulus was defined as target. When the target was an arrowhead the sub-

Table 1
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	L 125	11	L 375, C 4.5
2	L 250, Rop 2	12	L 187.5, Rop 6, A 300
3	L 437.5	13	L 187.5, Pr 1.05, E 600
4	Pr 0.804, A 200	14	L 125
5	L 447.5, C 2	15	L 325, C 4, S 10
6	L 500, C 6	16	Pe 3
7	L 600, C 4, E 1000, A 200	17	L 500, C 2
8	L 700, C 5.5, E 1000, A 400	18	Pr 2.5, S 5
9	L 50	19	Pr 2.1, Rot 4, A 300
10	L 600, Pr 0.54, E 800, S 5, A 300	20	L 400, Pe 4, S 7.5

Abbreviations: A, Amantadin; C, Cabergolin; E, Entacapon; L, L-DOPA; Pe, Pergolid; Pr, Pramipexol; Rop, Ropinirol; Rot, Rotigotin; S, Selegilin.

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

Patient	Medication (dose per day in mg)	Patient	Medication (dose per day in mg)
1	L 187	9	R 1, C 0.25
2	Rop 90	10	R 1
3	L 375, Rop 6	11	L 187.5
4	Pr 105	12	L 187.5, Rop 3
5	R 1	13	L 262.5
6	S 5, Rop 3	14	L 100, S 5, Pe 0.2
7	R 1, Pr 2, B 30	15	R 1
8	R 1, Rop 3, A 300		

Abbreviations: A, Amantadin; B, Budipin; C, Cabergolin; L, L-DOPA; Pe, Pergolid; Pr, Pramipexol; R, Rasagilin; Rop, Ropinirol; S, Selegilin.

jects had to press a button on the side the target pointed to; when the target was a circle, no response had to be given (Nogo trials). Above and below each target a flanker was presented which pointed either to the same side (congruent trials) or to the opposite side (incompatible trials) of the target. Nogo and incongruent trials had a probability of 20% each, congruent trials had a probability of 60%. By making the incongruent stimuli relatively rare we aimed at increasing interference and hence demands on response selection processes. Right and left pointing flankers were equiprobable. The flankers preceded the targets by 100 ms (Stimulus Onset Asynchrony, SOA = 100 ms) to further strengthen their influence and consequently further increase the demands on conflict monitoring and response selection. Flankers and targets were switched off 100 ms after target onset. The next flanker was presented 800–1200 ms (interval randomised) after the response of the subjects, or 1900–2300 ms after a Nogo target. Altogether 420 stimuli were presented in four blocks of 105 stimuli each, which were interrupted by short breaks. The subjects were asked to react as fast as possible to the arrowhead targets.

A response was given with one of two joystick-like vertical bars. Pressure-sensitive buttons were mounted at the top of the bars and had to be operated with the right and left thumb. A response was defined as such when the pressure reached a criterion value of 2.75 N. Time pressure was administered

Table 3
Descriptive data for the different groups of ages, sex, general level of intelligence (MWT-B), depression (BDI), Unified Parkinson's Disease Rating Scale (UPDRS motor score) and executive functions (WCST).

	Mean (S.D.)			
	Young ($n = 20$)	Elderly ($n = 32$)	De novo PD ($n = 15$)	Med. PD ($n = 20$)
Age (years)	24.0 (±2.5)	62.8 (±10.1)	59.6 (±10.4)	64.5 (±9.7)
Sex	8 female/12 male	14 female/18 male	8 female/7 male	8 female/12 male
MWT-B (IQ)	108.8 (±9.9)	124.3 (±14.4)	113.5 (±11.4)	126.9 (±10.4)
BDI	2.5 (±4.2)	5.3 (±6.6)	Pre med. 8.3 (±4.6) Post med. 8.0 (±3.7)	7.1 (±5.1)
UPDRS motor score	N/A	N/A	Pre med. 12.7 (±5.5) Post med. 8.7 (±3.9)	Off med. 14.8 (±5.3) On med. 10.8 (±5.6)
WCST				
Errors	12.8 (±5.3)	23.5 (±18.5)	32.9 (±24.1)	38.3 (±28.2)
Perseverative errors	6.4 (±2.6)	12.2 (±9.7)	17.5 (±18.5)	15.7 (±11.5)
Categories completed	6.0 (±0.0)	5.3 (±1.7)	4.4 (±2.4)	4.3 (±2.3)

by an individual deadline method; the deadline reaction time (RT) was determined for each subject by the mean individual RT and error rate in the flanker task in the training session. A feedback tone (1000 Hz) was presented 500 ms after the response, if the RT was slower than the deadline RT. The subjects were asked to respond fast enough to avoid the feedback tone.

2.3. EEG recording and analysis

During task performance the electroencephalogram (EEG) was recorded from 26 electrodes: Fp1, Fpz, Fp2; F7, F3, Fz, F4, F8; FC5, FC3, FCz, FC4, FC6; C3, Cz, C4; P7, P3, Pz, P4, P8; M1, M2; O1, Oz, O2. The vertical EOG was recorded from 4 electrodes above and below both eyes, and the horizontal EOG from 2 electrodes at the outer canthi of the eyes. The amplifier EPA-5 (Sensorium Inc.) was used. The forehead was used as ground. The primary reference was Cz. In addition to EEG and EOG, the response forces of both hands were measured, as outlined above. EEG, EOG and force data were sampled with 500 Hz (Acquire, Neuroscan Inc.) and stored continuously on a PC hard-disk together with stimulus and response markers. The data were analysed off-line. EEG segments beginning 200 ms before and ending 400 ms after the response were cut out and averaged separately for correct and error responses. The ERP data were re-referenced to average reference to make them independent on any specific reference such as the mastoid. The N2 was measured against the amplitude of the preceding P2, which was determined as the largest positive peak from 190 ms after target onset until the N2 peak. The N2 was quantified at electrode Fz and FCz, as these electrodes revealed the maximal N2, as can be seen in the scalp topography plots (Fig. 1). The P3 was quantified at electrodes Pz and Cz and defined as the most positive peak within the time window of 300–600 ms. Only trials with correct reactions were used for data analyses.

2.4. Statistical analysis

Behavioural parameters (reaction times RT, error rates) were analyzed in separate repeated measures ANOVAs with the within-subject factor "compatibility" (compatible vs. incompatible) and the between-subject factor "group".

The N2 and P3 (amplitudes and latencies) were analyzed in separate repeated measures ANOVAs with the within-subject factors "electrode" (Fz and FCz), "compatibility" (compatible vs. incompatible) and the between-subject factor "group".

To examine possible effects of medication in the PD and de novo PD group, the N2 and the P3 were subsequently analyzed using a second repeated measures ANOVA with the within-subject factors "electrode" (Fz and FCz), "compatibility" (compatible vs. incompatible) and "medication on/off; pre/post" and the between-subject factor "group".

All performed post hoc tests were Bonferroni-corrected and Greenhouse–Geisser correction was applied, where appropriate. All variables included into the analyses were normal distributed (all $z < 1$; $p > .2$; one-tailed). The mean and standard error of the mean are given ($M \pm$ S.E.M.).

3. Results

3.1. Behavioural data

For the reaction times (RT) the repeated measures ANOVA revealed a main effect "compatibility" ($F(1,83) = 1350.00$; $p < .001$): RTs were shorter in compatible (372.8 ± 5.9) than in incompatible trials (483.9 ± 6.3). There was also a main effect "group" ($F(3,83) = 27.94$; $p < .001$). Bonferroni-corrected post hoc tests showed that young controls revealed shortest RTs (335.2 ± 12.0) ($p < .001$). Elderly controls showed shorter RTs (433.5 ± 9.4) than de novo PDs pre-medication (485.2 ± 13.8) ($p < .001$), but did not differ from PD patients (459.5 ± 12.0) ($p > .5$). The latter group did also not differ from de novo PDs ($p > .9$). The compatibility effects did not differ between the groups, since there was no significant group × compatibility interaction.

Regarding the error rates there was only a main effect "compatibility" ($F(1,83) = 152.59$; $p < .001$), where it is shown that error rates were higher in the incompatible (16.5 ± 1.3), than in the compatible condition (1.1 ± 0.25).

3.2. Behavioural data – medication effects

Regarding possible medication effects in the PD and the de novo PD group the repeated measures ANOVA reveals that the main effect "medication on/off" was not significant ($F(1,33) = 1.05$; $p > .3$), while there was an interaction "medication by group" ($F(1,33) = 6.18$; $p = .018$). Bonferroni-corrected post hoc tests revealed that in de novo PDs RTs became faster post treatment (469.4 ± 17.1) (pre treatment: 485.2 ± 19.3) ($F(1,14) = 4.81$; $p < .05$). No difference was seen in PD patients measured on and off-medication (on: 459.5 ± 13.5; off: 466.1 ± 14.1) ($F(1,19) = 1.45$; $p > .2$). For the error rates there was no effect of treatment/medication (all F's < 0.6; $p > .4$).

3.3. Neurophysiological data

3.3.1. N2-effects

Regarding the amplitudes, a strong main effect "compatibility" is shown ($F(1,83) = 157.22$; $p < .001$), with the N2 being larger on incompatible (-2.45 ± 0.06) than on compatible trials (-1.49 ± 0.03). Furthermore, there was a main effect "electrode" ($F(1,83) = 9.42$; $p = .003$), with the N2 being larger at electrode FCz (-2.09 ± 0.7), compared to Fz (-1.84 ± 0.03). The N2 on compatible and incompatible trials is given in Fig. 1.

There was also a main effect "group" ($F(3,83) = 292.63$; $p < .001$). It is shown that the N2 was strongest in young

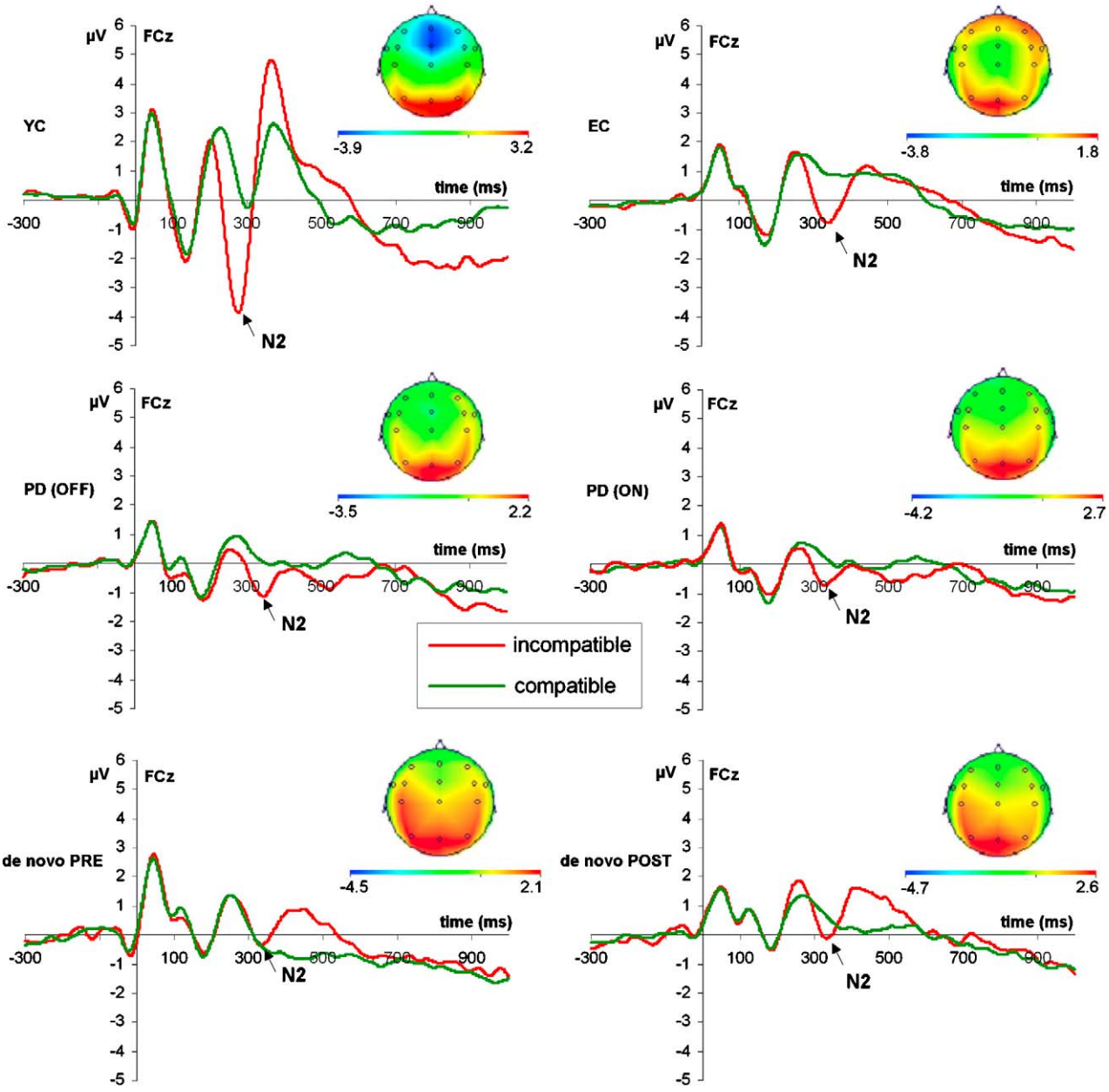

Fig. 1. Stimulus-locked ERPs on incompatible (red) and compatible (green) trials. Each group is denoted separately. For de novo PD group and the medicated PD group the ERPs pre and post-medication and off and on-medication, respectively are given. The maps for the N2 on incompatible trials are given (note the different scaling of the maps). Time point zero denotes the onset of the target. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

controls, differing from all other groups. Elderly controls and the PD groups did not differ from each other (see Fig. 2a).

There was an interaction "compatibility × electrode × group" ($F(3,83) = 6.36$; $p = .001$). Subsequent Bonferroni-corrected separate univariate ANOVAs for electrode Fz and FCz revealed that an interaction "compatibility × group" was only evident at electrode FCz ($F(3,83) = 16.01$; $p < .001$), but not at Fz ($F(3,83) = 1.1$; $p > .2$). Hence modulations between compatible and incompatible trials within each group were only analyzed at electrode FCz. Here it is shown (see Fig. 2b) that the initially diagnosed de novo PD group showed no N2 amplitude difference between compatible and incompatible trials ($F(1,14) = 0.8$; $p > .3$), while all other groups revealed a larger N2 on incompatible than on compatible trials (all F's > 48.6; $p < .001$). For incompatible S-R relations the groups differed in their N2 ($F(2,64) = 20.7$; $p < .001$). The N2 was larger in de novo PDs (-1.57 ± 0.10) than both other groups (elderly: -0.83 ± 0.07; PD (off): -0.79 ± 0.09) ($p < .001$). For compatible S-R relations the elderly groups did not differ in their N2 ($F(2,64) = 0.9$; $p > .3$).

Concerning the latencies, there was only a main effect "group" ($F(3,83) = 5.55$; $p = .002$): the young controls

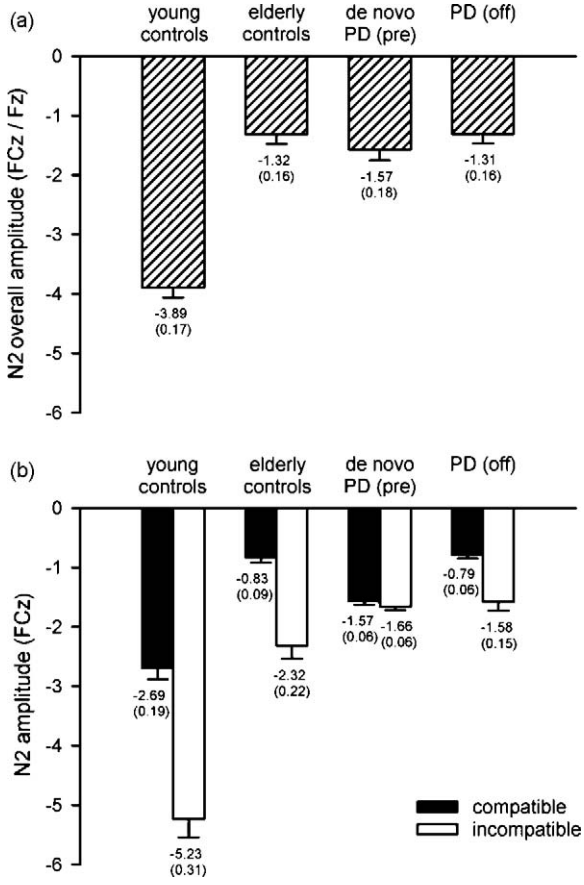

Fig. 2. (a) The overall N2 amplitudes across compatible and incompatible trials above electrodes FCz and Fz are given for each group separately. (b) The N2 amplitude at electrode FCz separated for compatible and incompatible trials for each group is given. As can be seen no difference is evident between the trial types in the de novo PD group pre-medication.

showed the shortest latencies (278.3 ± 12.5), differing from all other groups ($p < .001$) (elderly control: 338.5 ± 14.5; PD: 333.8 ± 12.5; de novo PD: 336.5 ± 14.5). The latter groups did not differ from each other. All other effects were not significant (all F's < 1.5; $p > .2$).

3.3.2. N2 – medication effects

Regarding possible medication effects in the PD and the de novo PD group the repeated measures ANOVA reveals that the factor "medication" was further modulated by the factors "electrode", "compatibility" and "group" ($F(1,33) = 7.26$; $p = .011$). To break this 4-way interaction down, each group was analyzed separately. For the PD group the interaction "electrode × compatibility × medication" was not significant ($F(1,29) = 2.37$; $p > .15$), but it was for the de novo PD group ($F(1,14) = 8.91$; $p = .010$). Hence, only the de novo PD group was analyzed further.

Here, the main effect "medication" was marginally significant ($F(1,14) = 3.42$; $p = .086$), but interacted with the factors "electrode" and "compatibility" ($F(1,14) = 8.91$; $p = .010$). Subsequent Bonferroni-corrected post hoc tests revealed an interaction "compatibility × pre-post" only for electrode FCz ($F(1,24) = 23.37$; $p < .001$), but not for Fz ($F(1,14) = 0.35$; $p > .5$). Hence only electrode FCz was analyzed further. While no difference between compatible and incompatible trials is seen in pre-medication, a difference between compatible and incompatible trials is seen in post-medication (see Fig. 3a) (pre-medication: $t = 0.850$; d.f. = 14; $p > .3$) (post-medication: $t = 4.57$; d.f. = 14; $p < .001$). However, it is shown that this effect is due to changes in the modulation during compatible trials ($t = -15.34$; d.f. = 14; $p < .001$), as no differences were seen in incompatible trials pre vs. post-medication

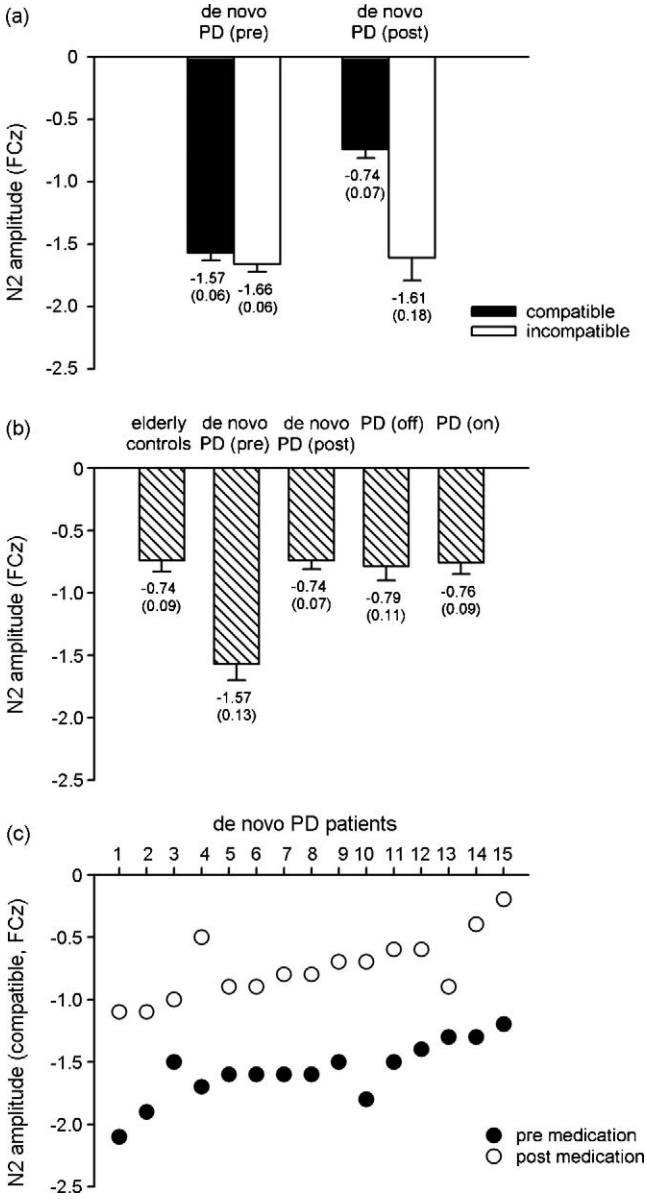

Fig. 3. (a) The amplitude of the N2 across compatible and incompatible trials at electrode FCz for the de novo PD group pre and post-treatment. As can be seen, treatment induces a difference in the modulation between the trial types. (b) Amplitudes of the N2 at electrode FCz across both trial types for all elderly groups. As can be seen, there is no difference between elderly controls and de novo post-treatment and the medicated PD group, irrespective of medication. (c) N2 amplitudes for each de novo PD patient for compatible trials only at electrode FCz.

($t = -0.306$; d.f. = 14; $p > .5$) (Fig. 3a). Pre-medication de novo PD group showed a larger N2 on compatible trials (-1.57 ± 0.13), than elderly controls (-0.74 ± 0.09) and PD off-medication (-0.79 ± 0.11) ($p < .001$) ($F(2,64) = 13.50$; $p < .001$).

Comparing de novo PDs post-medication with elderly controls and PD patients on and off-medication revealed no difference between the groups ($F(2,64) = 0.05$; $p > .8$) (Fig. 3b), suggesting a normalisation of neurophysiological processes during compatible trials post-medication. It is further shown that the N2 amplitude in compatible trials pre-medication was positively correlated with the modulation post-medication ($r = .645$; $R^2 = 0.41$; $p = .005$) (Fig. 3c). No other correlations were found (all r's $< .2$; $p > .3$). For the latencies, there was no medication effect (all F's < 1.8; $p > .2$).

3.3.3. P3-effects

Regarding the amplitudes the repeated measures ANOVA revealed a main effect "compatibility" ($F(1,83) = 19.86$; $p < .001$), with the P3 being larger on incompatible (4.81 ± 0.24) than on compatible trials (4.14 ± 0.28). Furthermore, there was a main effect "electrode" ($F(1,83) = 17.83$; $p < .001$) with the P3 being larger at Pz (5.21 ± 0.27) than and Cz (3.74 ± 0.33). Finally, there was a main effect "group" ($F(3,83) = 9.81$; $p < .001$): the P3 was largest in young controls (6.80 ± 0.50) and differed from all other groups ($p < .001$) (elderly control: 4.09 ± 0.40; PD: 3.24 ± 0.50; de novo PD (pre-medication): 3.77 ± 0.58). The latter groups did not differ from each other ($p > .8$). All other effects were not significant (all F's < 1; $p > .2$).

Regarding the latencies, there was also a main effect "compatibility" ($F(1,83) = 62.56$; $p < .001$), with latencies being longer for the incompatible (483.18 ± 8.39) than for the compatible condition (424.11 ± 8.24). Moreover the main effect "electrode" ($F(1,83) = 14.90$; $p < .001$) revealed that latencies were shorter at Pz (439.17 ± 8.43), than at Cz (468.11 ± 8.21). The interaction "electrode × compatibility" ($F(1,83) = 13.32$; $p < .001$) showed that compatibility effects were stronger at electrode Pz, compared to Cz ($p < .001$) (latency difference Pz: 87.1 ± 9.3; latency difference Cz: 38.6 ± 10.6). Finally there was a main effect "group" ($F(3,83) = 9.15$; $p < .001$). Young controls revealed the shortest latencies (387.9 ± 14.9) differing from all other groups ($p < .001$) (elderly control: 479.1 ± 11.8; PD: 478.9 ± 14.9; de novo PD (pre-medication): 468.6 ± 17.2). All other effects were not significant (all F's < 1; $p > .2$).

3.3.4. P3 – medication effects

There were no specific treatment effects (all F's < 1.3; $p > .2$).

4. Discussion

In the current study we examined aging, Parkinson's disease and medication effects on response selection and control processes. Doing this, we examined Parkinson's disease patients with a long history of medication and patients with initially diagnosed PD (de novo PD). These groups were complemented with healthy young and elderly controls. Both disease groups were examined twice. PD patients were examined on and off-medication; de novo PD patients were examined pre and post-medication.

The N2 results reveal that healthy elderly and young subjects differed in their modulation of the N2, being smaller for elderly subjects. Patients with longer dopaminergic treatment history showed similar modulations of the N2 compared to elderly subjects. This was independent if they are on or off-medicated. Pre-treatment patients with de novo PD differed from all other groups, since the N2 did not differ between compatible and incompatible trials. This effect is due to an enhancement of the N2 during compatible trials.

The P3 results reveal known effects of compatibility (Leuthold and Sommer, 1998) and age (e.g. Fjell et al., 2007; Kok, 2000) underlining the validity of the data. As no specific disease or treatment effects were obtained for the P3, these effects are specific for the N2.

4.1. N2-effects

As the N2 is suggested to depend upon the DA-system (Beste et al., 2008) the N2 difference in incompatible trials observed between healthy young and elderly controls is probably due to dysfunctions of the DA-system occurring during aging (Bäckman et al., 2006). However, besides the DA-system, striatal MSPs and the basal ganglia as a whole are important for action selection processes (Bar-Gad et al., 2003; Redgrave et al., 1999). Effective processing of striatal MSPs depends upon the functioning of the nigro-striatal DA-system (Gurney et al., 2004; Surmeier et al., 2007). As MSP neuron function and striatal volume decline with increasing age (Martella et al., 2008; Matochik et al., 2000) these processes may also influence declines of the N2 in the elderly.

Since a comparable attenuation of the N2 in incompatible S-R relations was seen in all elderly groups (i.e. PDs and healthy controls) these modulations are solely age specific and not modulated by disease. Functionally this attenuation in incompatible trials, where conflict and control is necessary, appears to reflect an attenuation of conflict processing or response control in PD. Alternatively, response control could be smaller in elderly simply because they have weaker incorrect response activations and hence reduced conflict. However, this is unlikely since elderly have rather enhanced incorrect response activations in the flanker task, as recently shown by our group (Wild-Wall et al., 2008).

Disease-specific effects, unbiased of any medication, are reflected in a lack of difference in neurophysiological modulations between compatible and incompatible trials in the de novo PD group pre-medication. This lack of difference is due to an intensification of response selection processes during compatible S-R relations. Response selection processes therefore seem to become equally demanding during com-

patible and incompatible trials in untreated patients with PD. Hence, de novo PD patients seem to encounter problems in response selection (Beste et al., 2008; Gajewski et al., 2008) even in easy, compatible S-R relations. The observed lack of difference between compatible and incompatible S-R relations in the de novo PD group pre-medication may suggest that these normally automated S-R conditions become less automated and therefore take more processing. This processing, however, may not be performed properly as the DA-system is dysfunctional. It can also not be ruled out that deficits in the integration of motor responses rely beyond these alterations.

As can be seen in de novo PDs, treatment affects specifically this disease-specific increase of the N2 in compatible trials, leading to a decreased N2 in compatible trials post treatment. Due to dopaminergic modulation response selection processes become more effective and compatible S-R relations less demanding. This is underlined by the behavioural data, showing a decrease in RTs post treatment. As these changes are already evident after 8-week treatment, treatment agonizing the DA-system is very effective to counteract effects of pathogenic processes on response selection functions in PD. The correlational data suggests (see also Fig. 3c) that the degree of neurophysiological changes observed post treatment (i.e. N2) directly depends upon the neurophysiological modulation pre treatment. Ongoing treatment may not further change this pattern. This is suggested by the picture displayed by the PD group with a history of medication, showing a small N2 during compatible trials, not differing from de novo PDs post treatment. It is most probable that a ceiling-effect is reached due to medication, because no difference to elderly controls is seen. Nevertheless, the results show that the treatment is able to counteract ongoing deterioration in PD (Dauer and Przedborski, 2003), leading to age-appropriate response selection functions.

As treatments agonizing the DA-system selectively affect response selection in compatible trials, but not in incompatible ones, processes related to response selection in the two conditions probably depend upon distinct neuronal mechanisms. Both, MSPs and the dopaminergic nigro-striatal system are affected in PD (Chase and Oh, 2000; Dauer and Przedborski, 2003) and are important for action selection processes (Bar-Gad et al., 2003; Redgrave et al., 1999). Even though it is suggested that processes of response selection depend upon both of these systems (Bar-Gad et al., 2003; Gurney et al., 2004; Surmeier et al., 2007) the treatment effects in de novo patients on the N2 suggest that the DA-system is predominantly important for response selection in compatible S-R conditions. Due to the observed insensitivity to dopaminergic treatment of response selection processes in incompatible S-R relations, these processes seem to be relatively independent of dopaminergic neural transmission. Both, the DA-system and MSPs are dysfunctional in all elderly groups (Bäckman et al., 2006; Chase and Oh, 2000; Dauer and Przedborski, 2003). However, as N2-effects seen in incompatible S-R relations are age specific and independent of the DA-system it may be speculated that response selection in incompatible S-R relations is predominantly mediated via MSPs or other brain areas, independent of dopaminergic modulation.

5. Conclusions

In the current study we examined the effects of aging and medication affecting the DA-system in Parkinson's disease on response selection processes. Medication selectively affected response selection in compatible S-R relations, which was pathologically enhanced in de novo patients. This effect was evident even after short-term treatment, not differing from long-term treatment. Contrary, age-related attenuations of the N2 in incompatible S-R relations, most probably reflecting impaired conflict processing or response control, are unaffected by treatment. The results suggest that the N2 reflects different processes in compatible and incompatible S-R relations that demand different neuronal mechanisms within in the basal ganglia. However, there may be some limitations of the study, which may be due to mixed forms and doses of medication within the de novo-PD and PD group. Furthermore, it may have been interesting to incorporate Racloprid-PET data to further monitor the effects of treatment.

Conflict of interest

None declared.

Acknowledgements

This work was supported by grant FA 211/16-1 to 3 from the Deutsche Forschungsgemeinschaft (DFG) and a grant from FoRUM AZ-F479-2005, Ruhr University Bochum. We thank Ludger Blanke, and Christiane Westedt for their help in setting up and conducting the experiments, and all participants for their participation.

References

Antal, A., Bandini, F., Keri, S., Bodis-Wollner, I., 1998. Visuo-cognitive dysfunctions in Parkinson's disease. Clin. Neurosci. 5 (2), 147–152.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci. Biobehav. Rev. 30 (6), 791–807.

Bar-Gad, I., Morris, G., Bergman, H., 2003. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. Prog. Neurobiol. 71 (6), 439–473.

Berman, S.M., Noble, E.P., Antolin, T., Sheen, C., Conner, B.T., Ritchie, T., 2006. P300 development during adolescence: effects of DRD2 genotype. Clin. Neurophysiol. 117 (3), 649–659.

Beste, C., Saft, C., Andrich, J., Gold, R., Falkenstein, M., 2006. Error processing in Huntington's disease. PLoS ONE 1, e86.

Beste, C., Saft, C., Andrich, J., Gold, R., Falkenstein, M., 2008. Stimulus-response compatibility in Huntington's disease: a cognitive-neurophysiological analysis. J. Neurophysiol. 99 (3), 1213–1223.

Botvinick, M.M., Cohen, J.D., Carter, C.S., 2004. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn. Sci. 8 (12), 539–546.

Ceponiene, R., Westerfield, M., Torki, M., Townsend, J., 2008. Modality-specificity of sensory aging in vision and audition: evidence from event-related potentials. Brain Res. 1215, 53–68.

Chase, T.N., Oh, J.D., 2000. Striatal dopamine- and glutamate-mediated dysregulation in experimental parkinsonism. Trends Neurosci. 23 (10), S86–S91.

Chudasama, Y., Robbins, T.W., 2006. Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. Biol. Psychol. 73 (1), 19–38.

Dauer, W., Przedborski, S., 2003. Parkinson's disease: mechanisms and models. Neuron 39 (6), 889–909.

Doucet, C., Stelmack, R.M., 1999. The effect of response execution on P3 latency, reaction time, and movement time. Psychophysiology 36, 351–363.

Falkenstein, M., Willemssen, R., Hohnsbein, J., Hielscher, H., 2006. Effects of stimulus-response compatibility in Parkinson's disease: a psychophysiological analysis. J. Neural Transm. 113 (10), 1449–1462.

Fjell, A.M., Walhovd, K.B., Fischl, B., Reinvang, I., 2007. Cognitive function, P3a/P3b brain potentials, and cortical thickness in aging. Hum. Brain Mapp. 28 (11), 1098–1116.

Frodl-Bauch, T., Bottlender, R., Hegerl, U., 1999. Neurochemical substrates and neuroanatomical generators of the event-related P300. Neuropsychobiology 40 (2), 86–94.

Gajewski, P.D., Stoerig, P., Falkenstein, M., 2008. ERP—correlates of response selection in a response conflict paradigm. Brain Res. 1189, 127–134.

Gurney, K., Prescott, T.J., Wickens, J.R., Redgrave, P., 2004. Computational models of the basal ganglia: from robots to membranes. Trends Neurosci. 27 (8), 453–459.

Kok, A., 2000. Age-related changes in involuntary and voluntary attention as reflected in components of the event-related potential (ERP). Biol. Psychol. 54 (1–3), 107–143.

Kopp, B., Mattler, U., Goertz, R., Rist, F., 1996. N2, P3 and the lateralized readiness potential in a nogo task involving selective response priming. Electroencephalogr. Clin. Neurophysiol. 99 (1), 19–27.

Leuthold, H., Sommer, W., 1998. Postperceptual effects and P300 latency. Psychophysiology 35, 34–46.

Martella, G., Spadoni, F., Sciamanna, G., Tassone, A., Bernardi, G., Pisani, A., Bonsi, P., 2008. Age-related functional changes of high-voltage-activated calcium channels in different neuronal subtypes of mouse striatum. Neuroscience 152 (2), 469–476.

Matochik, J.A., Chefer, S.I., Lane, M.A., Woolf, R.I., Morris, E.D., Ingram, D.K., Roth, G.S., London, E.D., 2000. Age-related decline in striatal volume in monkeys as measured by magnetic resonance imaging. Neurobiol. Aging 21 (4), 591–598.

Praamstra, P., Plat, F.M., 2001. Failed suppression of direct visuomotor activation in Parkinson's disease. J. Cogn. Neurosci. 13 (1), 31–43.

Praamstra, P., Stegeman, D.F., Cools, A.R., Horstink, M.W., 1998. Reliance on external cues for movement initiation in Parkinson's disease. Evidence from movement-related potentials. Brain 121 (1), 167–177.

Redgrave, P., Prescott, T.J., Gurney, K., 1999. The basal ganglia: a vertebrate solution to the selection problem? Neuroscience 89 (4), 1009–1023.

Surmeier, D.J., Ding, J., Day, M., Wang, Z., Shen, W., 2007. D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. Trends Neurosci. 30 (5), 228–235.

Van Veen, V., Carter, C.S., 2002. The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiol. Behav. 77 (4–5), 477–482.

Wild-Wall, N., Falkenstein, M., Hohnsbein, J., 2008. Flanker interference in young and older participants as reflected in event-related potentials. Brain Res. 1211, 72–84.

Wylie, S.A., Stout, J.C., Bashore, T.R., 2005. Activation of conflicting responses in Parkinson's disease: evidence for degrading and facilitating effects on response time. Neuropsychologia 43 (7), 1033–1043.