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

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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.

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-

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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-