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Research Report

Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers

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ABSTRACT

Humans need to monitor their actions continuously to detect errors as fast as possible and to adjust their performance to prevent future errors. This process of action monitoring can be investigated by measuring the error-related negativity (ERN), an ERP component elicited immediately after an error. In the current study, we investigated action monitoring after administration of the classic antipsychotic haloperidol (2.5 mg), the atypical antipsychotic olanzapine (10 mg), and the antidepressant paroxetine (20 mg), a selective serotonin reuptake inhibitor. Healthy volunteers ($N = 14$) were administered the three compounds and placebo in a randomized, double-blind, single-dose, four-way cross-over design. All participants performed a speeded two-choice reaction task, while event-related potentials and behavioral measurements were obtained. Both haloperidol and olanzapine significantly reduced ERN amplitudes. After paroxetine, the ERN was not different from placebo. N2 congruency effects were not affected by treatment condition. Only olanzapine demonstrated behavioral effects, namely a slowing of responses, an increase in error rates, and the absence of performance adjustments. The attenuated ERNs after the dopamine antagonist haloperidol are in line with the presumed role of dopamine in action monitoring. Haloperidol is thought to block dopaminergic signaling, thus reducing ERN amplitudes. On the other hand, the effects of olanzapine are mainly caused by its sedative side effects, leading to a decline in motivation and appraisal of errors. Finally, the absence of any effects after paroxetine suggests that serotonin transmission does not play a direct role in regulating mechanisms related to action monitoring.

1. Introduction

Since the discovery of a response-locked event-related potential (ERP) component associated with error commission (Falkenstein et al., 1991; Gehring et al., 1993), a rapidly growing number of studies have investigated action-monitoring processes by examining this so-called error-related negativity (ERN).

Initial experiments focused on the major factors that affect ERN amplitude, like the emphasis in the instruction on speed or accuracy (Falkenstein et al., 1995). More recently, drug effects on

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action monitoring have become a topic of interest because of the proposed role of the dopamine system in reward processing in general and in the generation of the ERN in specific (Holroyd and Coles, 2002). The reinforcement-learning theory by Holroyd and Coles argues that the ERN is generated when a predictive error signal that is carried by dopaminergic pathways arrives at the anterior cingulate cortex (ACC).

A number of studies have provided support for this dopaminergic involvement in the generation of the ERN. Previous work from our laboratory demonstrated enhanced ERN amplitudes after administration of the indirect dopamine agonist D-amphetamine (De Bruijn et al., 2004). Zirnheld et al. (2004) showed reduced ERNs after administration of the dopamine receptor antagonist haloperidol, and Tieges et al. (2004) demonstrated that caffeine, an adenosine receptor antagonist influencing dopaminergic neurotransmission, yielded larger ERNs. Finally, attenuated ERN amplitudes were demonstrated after alcohol intake (Ridderinkhof et al., 2002). Holroyd and Yeung (2003) suggested that this finding may be explained by the effect alcohol has on dopamine receptors. Recently, Riba et al. (2005) found enlarged ERNs after administration of the selective α_2-adrenoceptor antagonist yohimbine and concluded that the noradrenergic system might serve as a complementary source of modulation of the ERN, apart from to the dopamine system.

Next to the more specific investigation of dopaminergic involvement, the effects of sedative drug properties have been studied. Johannes et al. (2001) reported reduced ERN amplitudes but no behavioral changes after administration of the benzodiazepine oxazepam. Smaller ERN amplitudes as well as slower reaction times were found for both the benzodiazepine lorazepam (De Bruijn et al., 2004) and alprazolam (Riba et al., in press). Also, the attenuated ERN amplitudes found after alcohol intake might be explained by inhibitory effects of alcohol on the mediofrontal cortex (Ridderinkhof et al., 2002).

Knowledge on neurotransmitter systems involved in action monitoring is not only important for theoretical aspects but could also prove to be relevant for clinical practice. Alterations in action monitoring, as reflected in differences in ERN amplitudes, have been found in a variety of psychiatric disorders like schizophrenia (e.g., Bates et al., 2002), obsessive–compulsive disorder (Gehring et al., 2000), Tourette syndrome (Johannes et al., 2002), and borderline personality disorder (De Bruijn et al., in press). These disorders are generally treated with psychoactive medication, although the exact mechanisms of action by which these compounds produce their beneficial effects still remain largely unknown.

In the current study, we wanted to investigate possible effects of commonly prescribed antipsychotic and antidepressant drugs on action monitoring. For this aim, participants performed a speeded two-choice reaction task, and both behavioral measurements and ERPs were obtained. The study was set up as a four-way cross-over design in healthy volunteers, with the classic antipsychotic haloperidol, the atypical antipsychotic olanzapine, the antidepressant paroxetine, and a placebo.

Based on the presumed role of dopamine in action monitoring and the previously reported reduced ERNs (Zirnheld et al., 2004), we expected administration of haloperidol to result in reduced action monitoring. Attenuated ERNs were also expected after administration of olanzapine, as this antipsychotic not only blocks dopamine but also serotonin and histamine receptors leading to sedative side effects. Finally, the selective serotonin reuptake inhibitor paroxetine mainly affects serotonin neurotransmission and does not have a direct effect on dopamine pathways. Therefore, we did not expect to find any effect on action monitoring after administration of paroxetine.

Next to the response-locked ERN, we investigated the stimulus-locked N2 component, as well as different behavioral measures. The N2 is thought to reflect pre-response conflict (Yeung et al., 2004) or response inhibition (Kopp et al., 1996) as it is enlarged after incongruent trials compared to congruent ones. For this reason, the N2 is considered to be a measure of the need for online cognitive control. The so-called conflict theory poses that both the N2 and the ERN are reflections of the same underlying process, viz. response conflict monitoring. Support for this assumption of the conflict theory comes, for example, from studies demonstrating that the N2 is generated in the same area of the medial frontal cortex as the ERN (see, e.g., Yeung et al., 2004). The behavioral measures of interest were reaction times, error rates, and the presence of performance adjustments following errors, as reflected in post-error slowing (Rabbitt, 1966).

2. Results

2.1. *Behavioral analyses*

2.1.1. *Reaction times*

The mean reaction times for the different treatment conditions are depicted in Fig. 1. Overall analyses on correct responses demonstrated main effects for treatment condition [$F(3,39) = 13.86$, $P < 0.001$] and congruency [$F(1,13) = 133.03$, $P < 0.001$]. The interaction between treatment condition and congruency was not significant [$F(3,39) = 1.05$, $P = 0.375$]. The main effect of congruency was caused by slower reaction times to incongruent stimuli (371 ms) compared to congruent ones (342 ms). With regard to the main effect of treatment condition, simple contrasts compared to placebo (335 ms) showed that reaction times were slower for olanzapine [397 ms; $F(1,13) = 29.11$, $P < 0.001$], but not different after haloperidol

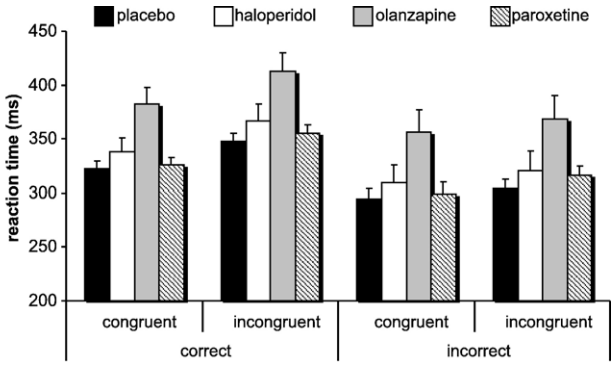

Fig. 1 – Mean reaction times for correct and incorrect responses to congruent and incongruent stimuli for the four treatment conditions. Error bars represent standard errors.