Dopamine modulates involuntary attention shifting and reorienting: an electromagnetic study

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Abstract

Objective: Dopaminergic function has been closely associated with attentional performance, but its precise role has remained elusive.

Methods: Electrophysiological and behavioral methods were used to assess the effects of dopamine D2-receptor antagonist haloperidol on involuntary attention shifting using a randomized, double-blind, placebo-controlled cross-over design. Eleven subjects were instructed to discriminate equiprobable 200 and 400 ms tones in a forced-choice reaction-time (RT) task during simultaneous measurement of whole-head magnetoencephalography and high-resolution electroencephalography.

Results: Occasional changes in task-irrelevant tone frequency (10% increase or decrease) caused marked distraction on behavioral performance, as shown by significant RT increases to deviant stimuli and subsequent standard tones. Furthermore, while the standard tones elicited distinct P1–N1–P2–N2–P3 waveforms, deviant tones elicited additional mismatch negativity (MMN), P3a, and reorienting negativity (RON) responses, indexing brain events associated with involuntary attention shifting. While haloperidol did not affect the source loci of the responses of magnetic N1 and MMN, the amplitude of the electric P3a and that of RON were significantly reduced and the latency of magnetic RON were delayed following haloperidol administration.

Conclusions: The present results suggest that dopamine modulates involuntary attention shifting to task-irrelevant deviant events. It appears that dopamine may disrupt the subsequent re-orienting efforts to the relevant task after distraction. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Attention; Auditory event-related responses; Dopamine; Electrocencephalography; Haloperidol; Magnetoencephalography

1. Introduction

Involuntary attention shifting is a fundamental function that helps one to orient to unexpected, potentially harmful changes in the environment (Sokolov, 1975), but needs to be controlled when concentrating on goal-directed functioning. Impaired control of involuntary attention shifting can cause pronounced distractibility and an inability to modify responses to external stimuli.

The neural basis of involuntary attention shifting can be studied non-invasively with high temporal resolution using event-related potentials (ERP) and event-related magnetic fields (ERF), which are time-locked changes due to external stimuli in the electroencephalogram (EEG) and magnetoencephalogram (MEG), respectively (Hari and Lounasmaa, 1989; Näätänen et al., 1994). MEG and EEG measure different aspects of electrical brain activity. The localization of cerebral activity is usually simpler and more accurate with MEG than with EEG. On the other hand, EEG shows the activity from subcortical sources that may not be detected with MEG (Hämäläinen et al., 1993). Simultaneous EEG and MEG recording thus provides high spatial and temporal resolution and make it possible to differentiate neural events related to involuntary perceptual processes better than either method alone.

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Recently, a paradigm was developed that yields distinct ERP and behavioral distraction effects with much smaller deviances than in traditional study designs (Schröger and Wolff, 1998a,b). In this paradigm, subjects have to discriminate between equiprobable long or short tones, which can be of high-probability standard frequency or of low-probability deviant frequency. These task-irrelevant frequency changes cause distraction on electrophysiological and behavioral level: they elicit a mismatch negativity (MMN) followed by P3a, and they prolong reaction times (RT) in the discrimination task. Moreover, task-irrelevant deviances elicit an additional frontocentral negativity with a latency around 400–600 ms (Schröger and Wolff, 1998a,b). This effect, referred to as the reorienting negativity (RON) (Schröger and Wolff, 1998a,b), has been proposed to reflect neural processing in the context of reorienting of attention following distraction.

The neurochemical regulation of involuntary attention shifting is not yet fully known. However, previous studies have shown that acute ethanol ingestion significantly reduces behavioral distractibility (Jahnsen et al., 1997), whereas the chronic effects have been documented to be opposite (Ahveninen et al., 2000a). A recent study indicated that a deficiency in the monoamine neurotransmitter serotonin induced by acute tryptophan depletions decreases MMN and N2b elicited by task-irrelevant deviants. The EEG results were accompanied by an increase of latencies of MMNm, the magnetic counterpart of MMN (Ahveninen et al., 2002). These studies indicate that attention shifting may be regulated by gamma amino butyric acid (GABA) and serotonin neurotransmitter systems.

The monoaminergic dopamine system may be associated with this fundamental function (Coull, 1998); however, its role has been scarcely studied. Attentional deficits were observed in disorders with presumed dopamine dysfunction such as in schizophrenia and Parkinson’s disease (Shelley et al., 1991; Vieregge et al., 1994; Michie et al., 2000). Haloperidol is a dopamine D2-receptor antagonist that is widely used for the treatment of schizophrenia. Acute administration of haloperidol changes dopaminergic activity in animals (Lidsky and Banerjee, 1993), in healthy subjects (Magliozzi et al., 1993), and in schizophrenic patients (Davidson et al., 1987; Davidson and Davis, 1988). Our previous studies have shown that haloperidol attenuates the processing negativity, an ERP component elicited by selectively attended standard tones, and it also increases the amplitude of MMN elicited by deviants in the unattended stimulus channel (Kähkönen et al., 2001a). These results, suggesting impaired selective attention, are supported by another finding indicating that haloperidol may also decrease the transient 40 Hz response to selectively attended tones (Ahveninen et al., 2000b). Our present study was designed to investigate with simultaneous MEG and ERP recordings whether changes in dopamine transmission induced by haloperidol affect involuntary attention shifting in healthy subjects.

2. Materials and methods

2.1. Subjects and design

A randomized, double-blind, placebo-controlled, cross-over design was used with a 2 mg oral dose haloperidol (Serenase<sup>®</sup> 1 mg tablet, Orion Pharma, Espoo, Finland) or placebo. Drugs were given to 11 right-handed healthy volunteers (aged 20–28 years; 6 females) after an institutional approval and an informed written consent were obtained. Dosage was chosen in accordance with studies showing that 2 mg of haloperidol affects cognitive performance without causing akathisia in healthy subjects (King, 1994). The drugs were administered 4 h before the measurements, because electrophysiological and positron emission tomography (PET) data have shown that the effects peak within 2–6 h after haloperidol administration in normal subjects (Barlett et al., 1994; Leigh et al., 1992; McClelland et al., 1990). The subjects were instructed to avoid alcohol for at least 48 h, and caffeine and tobacco for 12 h, prior to the recordings. The subjects reported having no history of neurological or psychiatric disorders or having used any drugs for 2 weeks before the study. None had been exposed to any class of neuroleptics previously. The hearing levels were confirmed by measuring the individual auditory thresholds. All experimental sessions were carried out between 8 and 12 a.m., and the sessions were separated by 1 week.

2.2. Stimuli and task

The stimuli were pure tones of either 200 or 400 ms in duration (including 10 ms rise and fall times) with an 1110 ms offset-to-onset interstimulus interval (ISI). The tone frequency, being 700 Hz for standard stimuli (\(P = 0.88\)) and either 630 or 770 Hz for deviant stimuli (\(P = 0.06\) for each), varied independently of the duration. The tones were randomly presented to left ear at 60 dB above the individually determined subjective hearing threshold. The subject was instructed to press as rapidly as possible a button with his left thumb to the 200 ms tones and another button with his right thumb to the 400 ms tones, and to ignore occasional frequency changes in the same tones. The stimuli were presented in two blocks to avoid fatigue, with resting periods of about 60 s between the blocks. RT and hit rates (HR) were measured to standards (excluding the first standard after a deviant), to deviants and to standards after deviant.

2.3. Data acquisition

During the MEG and EEG recordings, each subject sat in a comfortable chair in a magnetically and electrically shielded room (Euroshield Ltd, Finland). The ERF and ERP were recorded with a 122-channel whole-head MEG (4-D Neuroimaging Oy, Finland; Ahonen et al., 1993) and 64-channel EEG. Each two-channel sensor unit in MEG
measured two independent magnetic field gradient components $\partial B_z/\partial x$ and $\partial B_z/\partial y$, the z-axis being normal to the scalp. The position of the subject’s head relative to the recording instrument was determined by measuring the magnetic fields produced by marker coils in relation to cardinal points of the head (nasion, left and right pre-auricular points) that were located before the experiment using an Isotrak 3D-digitizer (Polhemus, Colchester, VT, USA; Ahlfors and Ilmoniemi, 1989). ERPs were recorded with an electrode cap (Virtanen et al., 1996) and an amplifier (Virtanen et al., 1997) specifically designed and built for simultaneous EEG and MEG measurements. The nose electrode was used as a reference. Vertical and horizontal electro-oculograms (EOG) were recorded. The locations of the EEG electrodes and the marker coils in relation to the cardinal points on the head were determined with the digitizer. The recording passband was 0.03–100 Hz for EEG and MEG and 0.5–30 Hz for EOG. The sampling rate was 394 Hz. Digital band-pass filtering was performed off-line at 1–30 Hz for N1/N1m and MMN/MMNm and 0.5–30 Hz for P3a/P3am and RON/RONm. The analysis period for averaged epochs was 750 ms (including a 100 ms pre-stimulus baseline). The first 20 responses and all the epochs coinciding with EOG, EEG, or MEG changes exceeding 100 $\mu$V, 150 $\mu$V, or 3000 fT/cm, respectively, were omitted from averaging. At least 100 responses (25 for each deviant subset) for the deviants were averaged. The ERP/ERF peaks were obtained from the latency ranges of 80–150 ms for N1/N1m, 130–250 ms for MMN/MMNm, 250–500 ms for P3a and P3am, and 480–550 ms for RONm. The time window from 450 to 550 ms was used for RON. The responses were judged significant when their peak amplitudes were larger than two times the standard deviations (SD) of the pre-stimulus noise.

2.4. Data analysis

ERPs and ERFs were averaged separately for standard and deviant stimuli. The deviance-related ERPs and ERFs were measured from subtraction curves (the pooled deviant-stimulus response minus standard-stimulus response). The ERP peak latencies and amplitudes were measured from the channel pair showing the highest amplitude over the left and right temporal areas. Left monaural stimulation is known to elicit an MEG signal over both the right and left auditory cortices (Pekkonen et al., 1995). The amplitudes and sources of N1m and MMNm were estimated with single equivalent current dipoles (ECD), determined by a least-squares fit for a fixed subset of 34 channels separately over each hemisphere from the orthogonal sensor pair $(|\partial B_z/\partial x|^2 + |\partial B_z/\partial y|^2)^{1/2}$. Dipole fits with at most 30% residual variance were considered successful. A spherical head model was used for source modeling. The N1, MMN, P3a, and RON peak amplitudes were measured manually from the channels: F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2, P1, Pz, and P2. Latencies were measured at the FCz electrode location for MMN, P3a, and RON and at the Cz for N1. Weighted mean amplitudes were used for analysis. The EEG data of two subjects was rejected because of technical reasons.

The effects of haloperidol on N1m, MMNm, P3am, and RONm amplitudes were tested by two-way (drug by hemisphere) repeated measures analyses of variance (ANOVA). The effect of haloperidol was analyzed on weighted mean amplitudes of N1, MMN, P3a, and RON by two-way (drug by electrodes) repeated measures ANOVAs. RTs were correlated with latencies of P3a and RON using Spearman correlation. Paired and unpaired $t$ tests were also used when appropriate.

3. Results

3.1. Behavioral data

Under placebo, deviants produced a significant prolongation of RT compared with standard sounds ($t = -5.5$, $P = 0.0004$) and standards after deviants ($t = -4.0$, $P = 0.002$). Haloperidol prolonged RT to standards, to deviants and standards after deviants compared to placebo but these differences were not significant ($t = -0.98$, $P > 0.05$; $t = -0.20$, $P > 0.05$; $t = -0.35$, $P > 0.05$, respectively). No differences were found in HR to standards and deviants after haloperidol and placebo conditions (Table 1).

3.2. MEG results

Fig. 1 shows the MEG responses of one representative subject. Results are summarized in Table 2. ANOVA revealed that haloperidol had a significant drug-by-hemisphere interaction [$F(1,10) = 8.2$, $P = 0.04$] on RONm latency. Other main effects were insignificant. Haloperidol had no significant effects for dipole moments of N1m or MMNm over both hemispheres. Nor did it affect the locations of N1m and MMNm (Table 3).

<table>
<thead>
<tr>
<th>Reaction times and hit rates after haloperidol and placebo administrations</th>
<th>Haloperidol (mean ± SD)</th>
<th>Placebo (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT (ms)</td>
<td>Standards</td>
<td>624 ± 22</td>
</tr>
<tr>
<td></td>
<td>Deviants</td>
<td>655 ± 22</td>
</tr>
<tr>
<td></td>
<td>Standards after deviants</td>
<td>642 ± 24</td>
</tr>
<tr>
<td>RT lag (ms) to standards after deviants</td>
<td>31 ± 9</td>
<td>39 ± 7</td>
</tr>
<tr>
<td>HR (%)</td>
<td>Standards</td>
<td>94 ± 1</td>
</tr>
<tr>
<td></td>
<td>Deviants</td>
<td>94 ± 1</td>
</tr>
<tr>
<td></td>
<td>Standards after deviants</td>
<td>94 ± 2</td>
</tr>
</tbody>
</table>
Fig. 1. MEG response (subtraction curves) in one subject measured during haloperidol (solid lines) and placebo (dotted lines) administration. The stimuli were delivered to the left ear. The enlarged response on the right is from the channel showing largest responses over the right temporal area (contralateral to the ear stimulated). On the bottom, the arrows depict the orientation and loci of single ECD of the MMNm response.
Table 2
N1m, MMNm, P3am, and RONm amplitudes and latencies after haloperidol and placebo administrations

<table>
<thead>
<tr>
<th>Component</th>
<th>Hemisphere</th>
<th>Amplitude (μV/cm)</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1m</td>
<td>Contralateral</td>
<td>66 ± 14</td>
<td>99 ± 2</td>
</tr>
<tr>
<td>N1m</td>
<td>Ipsilateral</td>
<td>37 ± 4</td>
<td>111 ± 4</td>
</tr>
<tr>
<td>MMNm</td>
<td>Contralateral</td>
<td>66 ± 23</td>
<td>191 ± 44</td>
</tr>
<tr>
<td>MMNm</td>
<td>Ipsilateral</td>
<td>49 ± 22</td>
<td>196 ± 58</td>
</tr>
<tr>
<td>P3am</td>
<td>Contralateral</td>
<td>45 ± 21</td>
<td>325 ± 73</td>
</tr>
<tr>
<td>P3am</td>
<td>Ipsilateral</td>
<td>40 ± 22</td>
<td>300 ± 60</td>
</tr>
<tr>
<td>RONm</td>
<td>Contralateral</td>
<td>32 ± 15</td>
<td>533 ± 71</td>
</tr>
<tr>
<td>RONm</td>
<td>Ipsilateral</td>
<td>35 ± 19</td>
<td>503 ± 89</td>
</tr>
</tbody>
</table>

3.3. EEG results

The standard tones elicited distinct P1–N1–P2–N2–P3 waveforms and deviant tones elicited additional MMN, P3a, and RON responses (Figs. 2 and 3). EEG results are summarized in Table 4. A significant main effect was found in the RON amplitudes \[ F(1,8) = 10.0, P = 0.01 \]. The ANOVA showed a significant drug-by-electrode interaction \[ F(1,8) = 5.0, P = 0.05 \] on RON amplitudes and a significant drug-by-electrode interaction \[ F(1,8) = 13.2, P = 0.007 \] on P3a amplitudes. The post-hoc paired \( t \) test showed that haloperidol significantly decreased the P3a amplitudes at parietal electrodes \( t = 3.6, P = 0.007 \). Haloperidol significantly decreased the RON amplitudes at frontocentral and central electrodes \( t = 2.5, P = 0.03 \) and \( t = 3.1, P = 0.01 \), respectively. Haloperidol did not affect the latencies of N1, MMN, P3a, and RON. The RT to deviant tones correlated positively with the latencies of P3a in the haloperidol condition \( \sigma = 0.67, P = 0.05 \), but not in the placebo condition. No significant correlations between the RT and the latencies of RON were observed.

4. Discussion

The present data suggest a specific pattern of changes by haloperidol in ERP and ERF components elicited by task-irrelevant deviant events. The single dose of (2 mg) of this dopamine antagonist did not significantly affect the behavioral accuracy of the subjects. One of the most profound effects was the RON amplitude decrement, which was accompanied by the peak-latency delay in RONm. RON, being maximal at frontocentral EEG electrodes, is elicited by task-irrelevant deviances and is suggested to be generated by multiple generators in frontal and centroparietal brain regions (Schröger et al., 2000). Its physiological role is not yet well characterized, but earlier EEG studies with the present distraction paradigm suggest that RON reflects neural processing related to attention reorienting following distraction (Schröger and Wolff, 1998a,b; Schröger et al., 2000). The RON/RONm findings thus suggest that the modulation of dopamine transmission by haloperidol may impair the switching of attention back to the relevant task after distraction. However, haloperidol is known to bind with high affinity to sigma receptors (Weisman et al., 1988). Therefore it is possible that some of the observed effects in dopamine D2-poor areas reflect direct binding at non-dopaminergic sites.

The present study also indicated a significant reduction of P3a amplitude by haloperidol. This ERP component, being usually maximal over the central and frontal scalp areas, is presumed to reflect attention switching to irrelevant tones (Sams et al., 1985; Grillon et al., 1990, Woods, 1992; Escera et al., 1998). It has been proposed that P3a has two main sources: the source responsible for the early part of P3a would be located in the superior temporal cortex (Alho et al., 1998) and the later part would be generated in the pre-frontal cortex (Baudena et al., 1996). In the present study, haloperidol effects on P3a amplitude were, however, mainly observed in the parietal areas. This suggests that haloperidol...
effects may have been mediated by other than frontal or supratemporal P3a sources, localized at the parietal, parahippocampal, and anterior cingulate regions by intracranial recordings (Alain et al., 1989; Baudena et al., 1996; Halgren et al., 1995; Kropotov et al., 1995).

Finally, no significant haloperidol effects were observed.
in MMN/MMNm, which is surprising in the light of our earlier findings (Kähkönen et al., 2001a). This discrepancy may, however, be caused by the fact that, the stimulation and task parameters were different. No effects were indicated in N1/N1m responses generated mainly near the primary auditory cortices (Hari et al., 1980), which basically

Fig. 3. Grand-averaged subtraction waveforms after haloperidol and placebo administration. Negativity is upward.
Table 4
N1, MMN, P3a, and RON indices following haloperidol and placebo administration.

<table>
<thead>
<tr>
<th>ERP deflection</th>
<th>Electrode</th>
<th>Amplitude (mV)</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Haloperidol</td>
<td>Placebo</td>
</tr>
<tr>
<td>N1</td>
<td>Fz</td>
<td>−2.6 ± 1.4</td>
<td>−2.7 ± 1.2</td>
</tr>
<tr>
<td>N1</td>
<td>FCz</td>
<td>−2.9 ± 1.7</td>
<td>−3.0 ± 1.4</td>
</tr>
<tr>
<td>N1</td>
<td>Cz</td>
<td>−3.0 ± 1.9</td>
<td>−3.2 ± 1.6</td>
</tr>
<tr>
<td>N1</td>
<td>Pz</td>
<td>−2.8 ± 1.9</td>
<td>−2.8 ± 1.4</td>
</tr>
<tr>
<td>MMN</td>
<td>Fz</td>
<td>−2.7 ± 1.2</td>
<td>−2.6 ± 1.0</td>
</tr>
<tr>
<td>MMN</td>
<td>FCz</td>
<td>−2.7 ± 1.8</td>
<td>−2.5 ± 1.2</td>
</tr>
<tr>
<td>MMN</td>
<td>Cz</td>
<td>−2.4 ± 2.0</td>
<td>−1.8 ± 1.3</td>
</tr>
<tr>
<td>MMN</td>
<td>Pz</td>
<td>−2.1 ± 2.3</td>
<td>−1.5 ± 1.6</td>
</tr>
<tr>
<td>P3a</td>
<td>Fz</td>
<td>3.7 ± 1.8</td>
<td>3.9 ± 1.7</td>
</tr>
<tr>
<td>P3a</td>
<td>FCz</td>
<td>4.3 ± 2.2</td>
<td>4.8 ± 2.2</td>
</tr>
<tr>
<td>P3a</td>
<td>Cz</td>
<td>4.1 ± 2.5</td>
<td>5.3 ± 2.4</td>
</tr>
<tr>
<td>P3a</td>
<td>Pz</td>
<td>3.2 ± 2.1</td>
<td>4.9 ± 2.2**</td>
</tr>
<tr>
<td>RON</td>
<td>Fz</td>
<td>−0.2 ± 1.8</td>
<td>−0.6 ± 2.4</td>
</tr>
<tr>
<td>RON</td>
<td>FCz</td>
<td>−0.3 ± 1.9</td>
<td>−0.9 ± 2.9*</td>
</tr>
<tr>
<td>RON</td>
<td>Cz</td>
<td>−0.7 ± 2.6</td>
<td>−0.6 ± 2.9**</td>
</tr>
<tr>
<td>RON</td>
<td>Pz</td>
<td>−1.0 ± 3.2</td>
<td>−0.6 ± 3.0</td>
</tr>
</tbody>
</table>

* Paired t test between haloperidol and placebo conditions; **P < 0.05. ***P < 0.01.

supports earlier observations that the role of the central dopamine system is not crucial in the early auditory-cortical stimulus processing (e.g. Kahkonen et al., 2001b).

PET studies have shown that haloperidol alters metabolic activity in subcortical and cortical areas. Barlett et al. (1994) showed with PET that 5 mg of haloperidol reduces glucose utilization in frontal, occipital, and anterior cingulate cortex, whereas the effect is the opposite in the putamen and cerebellum. They suggested that haloperidol produces the effects in the striatum and other D2-rich areas. This could lead to increased inhibition of the thalamus through increased activity in GABA projections to globus pallidus and thalamus. Reduced activity from the thalamus could contribute to reduced neocortical activity. Notably, these brain regions that indicate the most profound metabolic changes by haloperidol are also suggested to be crucial for attention and executive cognitive functions. Tentatively, the present reductions in P3a and RON/RONm, suggesting impairments in neural processes underlying involuntary attention shifting and reorienting, may thus be mediated by haloperidol effects on the above-mentioned neuronal networks connecting the basal ganglia and pre-frontal brain regions.

In conclusion, our combined MEG and EEG results, demonstrating haloperidol-induced modulation of auditory evoked responses, suggest that dopamine modulates involuntary attention shifting and reorienting. The findings might also be associated with deficits observed in psychiatric and neurological disorders with dopamine abnormalities.

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