

No effects of l-dopa and bromocriptine on psychophysiological parameters of human selective attention

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Abstract

Patients with schizophrenia exhibit diverse cognitive deficits, one of which is a loss of the ability to focus attention. According to the revised dopamine hypothesis of schizophrenia both an increased mesolimbic and a decreased prefrontal dopaminergic activity is suggested to be involved in schizophrenia. The current study was designed to explore the relationship between dopamine and two psychophysiological parameters of selective attention, i.e. P300 amplitude and processing negativity (PN) in healthy volunteers.

In two separate experiments, with a double-blind, balanced and placebo-controlled crossover design, 18 healthy male volunteers were orally administered either 300 mg l-dopa (precursor of dopamine) or placebo (experiment I), or 1.25 mg bromocriptine (D2 agonist) or placebo (experiment II). Following this treatment they were tested in an auditory, dichotic selective attention paradigm.

An increase in P300 amplitude was found following deviant stimuli

when compared to standard stimuli and following attended stimuli when compared to unattended stimuli, regardless of treatment. Similarly, PN was found regardless of treatment. Neither l-dopa nor bromocriptine affected task performance or the amplitudes of PN or P300.

In the present study neither l-dopa nor bromocriptine affected PN, P300 amplitude or task performance in healthy controls, phenomena which are usually found to be disrupted in schizophrenia. This indicates that P300 amplitude and PN are neither affected by a global (l-dopa) increased dopaminergic activity, nor by a more selectively towards striatal areas targeted (bromocriptine) increase in dopaminergic activity.

Keywords

dopamine, l-dopa, bromocriptine, selective attention, P300, processing negativity, auditory oddball task

Introduction

Patients with schizophrenia exhibit diverse cognitive deficits when compared to healthy controls (Green, 1998). One of these deficits is a loss of the ability to respond adequately to novel stimuli, which is reflected in a reduced ability to detect infrequent stimuli in a sequence of frequent stimuli (Baribeau-Braun *et al.*, 1983; Strandburg *et al.*, 1999; Kayser *et al.*, 2001). Furthermore, from the early start of research on schizophrenia it is known that these patients are less able to direct their attention to one of several sources of incoming information than healthy controls (Kraepelin, 1913; McGhie and Chapman, 1961; see also Green, 1998). In

other words: patients with schizophrenia exhibit a loss of selective attention. One of the methods to study selective attention is by means of electrophysiology, e.g. by assessment of processing negativity (PN) or the P300 amplitude.

Processing negativity is suggested to reflect the mechanism for selectively attending to stimuli, defined by certain features (e.g. male/female voice, left/right ear) (Näätänen, 1990). Processing negativity appears most prominently in the (pre-) frontal areas of the brain (Woods, 1990), although a variety of generators seem to contribute, e.g. primary and secondary auditory cortex, anterior cingulate cortex, superior parietal lobe/supramarginal gyrus and the dorsolateral frontal cortex (Sevostianov *et al.*, 2002). Patients

with schizophrenia have frequently been found to show reduced PN, either with (Baribeau-Braun *et al.*, 1983; Iwanami *et al.*, 1998; Strandburg *et al.*, 1999) or without (Michie *et al.*, 1990; Ward *et al.*, 1991) medication. Furthermore, there is some evidence indicating that the amplitude of the PN correlates negatively with both positive and negative symptomatology of schizophrenia (Ward *et al.*, 1991).

A P300 amplitude is elicited by infrequent stimuli (deviants) appearing in a sequence of frequent stimuli (standards). Maximum P300 amplitude is commonly found when the subject is requested to respond to these deviant stimuli, e.g. by pressing a button. Roth and Cannon (1972) found a reduced P300 amplitude in patients with schizophrenia, when compared to healthy controls, a result which has been replicated in many studies since (e.g. Baribeau-Braun *et al.*, 1983; Michie *et al.*, 1990; Javitt *et al.*, 1995; Shutara *et al.*, 1996; Boutros *et al.*, 1997). The P300 amplitude seems to be trait-dependent (Juckel *et al.*, 1996), and seems to have a predictive value on the clinical outcome in terms of social functioning of schizophrenic patients (Strik *et al.*, 1996). Furthermore, sub-components of the P300, separated with dipole modelling, seem to be affected in a different manner by positive and negative symptoms (Frodl Bauch *et al.*, 1999b). Usually, P300 amplitude is maximal at parietocentral electrode sites, although, similarly to PN, a variety of generators seem to contribute to the P300 evoked related potential (ERP), e.g. left hemispheric temporal, bilateral frontal and parietal areas of the brain (Frodl Bauch *et al.*, 1999a; Muller *et al.*, 2001).

In the initial version of the dopamine hypothesis of schizophrenia, an association between schizophrenia and hyperactivity of the mesolimbic dopaminergic system was presumed. More recently, this hypothesis was revised and currently it is presumed that the positive symptoms of schizophrenia are associated with raised levels of mesolimbic dopaminergic activity, while negative symptoms are related to reduced levels of prefrontal dopaminergic activity (for reviews, see Kahn and Davidson, 1995; Duncan *et al.*, 1999; Nieoullon, 2002; Laruelle *et al.*, 2003). Speculatively therefore, both a hyperactive mesolimbic and a hypoactive prefrontal dopaminergic system might be involved in the reduction of selective attention, as observed in patients with schizophrenia. Indeed, in recent studies evidence is found that reduced dopaminergic transmission disrupts selective attention (Shelley *et al.*, 1997; Kahkonen *et al.*, 2001), which, in the light of the revised dopamine hypothesis of schizophrenia, would suggest a prefrontal dopaminergic modulation of selective attention. Furthermore, McKetin *et al.* (1999) report an improved selective attention following administration of amphetamine to healthy volunteers, albeit in an indirect way: they found reduced PN to location and pitch irrelevant stimuli in both the attended and unattended location in healthy volunteers following administration of 10 and 20 mg d-amphetamine. Similarly, they found a significant increase in P300 amplitude at lead Cz, but not Pz, which is the lead at which maximum P300 amplitude is normally found (Frodl Bauch *et al.*, 1999a). However, since amphetamine leads to a simultaneous raise in dopaminergic, noradrenergic and serotonergic activity throughout the brain (e.g. Kruk and Pycocock, 1991), it is unclear to what extent this increase in amplitude of P300 and PN was due to increased dopaminergic activity.

The present study was designed to further explore the relationship between the dopaminergic system and human selective attention, by studying the effect of increased dopaminergic activity on task performance and the amplitudes of the PN and P300 in healthy volunteers. In a first experiment, the effects of l-dopa (a precursor of dopamine, which raises dopamine activity throughout the brain) on these parameters were explored, while a second experiment explored the effects of a dopamine receptor agonist that targets the striatum more selectively. Since the dopamine D2 receptor is primarily present in the striatum, (e.g. Nieoullon, 2002), bromocriptine (a relatively specific postsynaptic D2 receptor agonist) was chosen. In both experiments two separate groups of 18 healthy male volunteers participated in a double-blind, placebo-controlled and balanced crossover design. To assess the effect of treatment on the dopaminergic system, plasma prolactin and homo-vanillic acid (HVA, the metabolite of dopamine) levels were determined. Since dopamine inhibits prolactin secretion, a reduced plasma prolactin level was expected in both experiments. Furthermore, in the case of l-dopa treatment an additional increase of plasma HVA was expected, as a result of an increased dopamine turnover.

Methods

Overall design

In two separate experiments l-dopa and bromocriptine were administered to healthy male volunteers, in a balanced, double-blind, placebo-controlled crossover design. Psychophysiological (prepulse inhibition of the startle reflex (PPI), P50 suppression and selective attention), neuro-endocrine (prolactin and cortisol), physiological (blood pressure and heart rate) and biochemical (HVA) data were collected over a 4.5-hour period during each session. In addition, two psychometric tests were administered: the Brief Psychiatric Rating Scale (BPRS) and the Visual Analogue mood Scale (VAS). The results of the PPI and P50 reduction tasks, cortisol levels, physiological data and the psychometric tests mentioned above have been reported elsewhere (Oranje *et al.*, 2004). From here on, the l-dopa experiment will be referred to as experiment I and the bromocriptine experiment as experiment II. The reader can assume that no differences are present in the designs of the two experiments, except when indicated.

Subjects

Healthy male volunteers were recruited through university newspaper advertisements. Only physically healthy subjects without any history, either personal or in first-degree relatives, of psychiatric illness were included. The study was approved by the Human Ethics Board of the University Medical Centre Utrecht, with respect to the statements made on human research in Helsinki. After written and oral information about the study had been given, written informed consent was obtained from all subjects before enrolment in the study. Subsequently, the subjects were interviewed, using the Comprehensive Assessment of Symptoms and

History (CASH) (Andreasen *et al.*, 1992) and the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) (Endicott and Spitzer, 1978) to assess for psychiatric illnesses. They also underwent a full physical examination including an electrocardiogram and routine laboratory tests (complete blood count, urine analysis and a urine toxicology screening for drug use). In addition, volunteers were screened for hearing deficits with an audiometer at 500, 1000 and 6000 Hz. Volunteers who could not detect tones at 20 dB were excluded.

Of the 20 subjects initially included in experiment I, seven subjects became severely nauseated (during the l-dopa treatment), of whom two were unable to complete the experiment. In addition, one subject had to be excluded for falling asleep during testing (during a placebo session). This resulted in 17 subjects with a mean age of 22.8 (SD = 2.95). From two subjects blood sampling could not be completed, while from a third one sample could not be analysed in the HVA assessment.

From the 18 subjects who were initially included in experiment II, one subject was excluded because of positive urine screening for Cannabis use. Six subjects became lightly nauseated or dizzy (in the bromocriptine treatment) yet were able to complete the experiments. This resulted in 17 subjects with a mean age of 22.9 (SD = 2.01).

Experimental design

Both experiment I and II had similar designs, apart from the temporal adjustments that were necessary as a result of the difference in pharmacokinetics of l-dopa and bromocriptine: the psychophysiological assessments started at the moment the peak plasma levels of both l-dopa (Cedarbaum *et al.*, 1989; Dempski *et al.*, 1989; LeWitt *et al.*, 1989; Yeh *et al.*, 1989; Robertson *et al.*, 1991) and bromocriptine (del Pozo *et al.*, 1986; Drewe *et al.*, 1988; Kopitar *et al.*, 1991) were to be expected, i.e. 2.5 h after oral intake of l-dopa and 1.5 h after oral intake of bromocriptine. Blood sampling, followed by the physiological assessments took place at appropriate intervals between the start of the experiment (8.45 AM) and the end, i.e. 1 hour after the psychophysiological assessments in both experiments (see below). Furthermore, in experiment I, the usefulness of l-dopa as a precursor of central dopamine was enhanced by the co-administration of carbidopa, which is an inhibitor of l-amino acid decarboxylase (L-AAD) and is not able to pass the blood-brain barrier. In the absence of carbidopa, much of the administered dose of l-dopa would eventually be destroyed by L-AAD in the liver and kidneys, and subsequently would not reach the brain. In addition, co-administration of carbidopa decreases side effects, since most of these effects are induced by the peripheral activity of dopamine (Frazer *et al.*, 1994). Carbidopa (50 mg) was taken orally every 8 h, (150 mg total) on the day preceding the experimental day, as well as in combination with l-dopa on a test day.

Subjects arrived at the research ward of the Department of Psychiatry, University Medical Centre Utrecht at 8.15 AM, having fasted since 11.00 PM the preceding day. An indwelling venous catheter was inserted into the antecubital vein of the left arm. The catheter was kept open with 1 ml heparin (100 Units/ml), infused after each blood sample. At 8.45 AM the medication (active or

placebo) was administered orally. In the case of l-dopa this consisted of two capsules containing tablets of Sinemet®: one tablet 125 CR and one tablet 250 CR (controlled release), containing 100 mg l-dopa with 25 mg carbidopa and 200 mg l-dopa with 50 mg carbidopa respectively. In the case of bromocriptine the medication was Parlodel®: one capsule, containing a tablet of 1.25 mg bromocriptine. In the case of placebo an identical number of capsules was administered as in the active treatment, however containing no active compounds (candy, with a remarkably similar appearance to the active medications). Psychophysiological assessments started with the subjects being brought to a sound-proof, electrically-shielded experimental cabin, where they were seated in a dentist's chair. To prevent data contamination through movement of the head or neck a vacuum cushion was attached to the top of the chair, to restrain the subject's head.

During each test session three tasks were presented: PPI, P50 suppression and an auditory selective attention task. The order of the tasks was balanced across the subjects. Blood samples, immediately followed by the physiological assessments, were collected at 0, 60, 120, 180, 205, 240 and 300 min following medication intake in experiment I (l-dopa) and at 0, 60, 90, 120, 150 and 210 min following medication intake in experiment II (bromocriptine). Blood samples were collected in 10 ml plastic tubes containing ethylene-diamine-tetra acetic acid (EDTA). They were centrifuged (10 min at 3000 rev/minute at 4°C) and stored at -80°C until the time of the assays.

Selective attention task

Between the two experiments, it was decided to alter the task slightly, to enable examination of task difficulty. Therefore, in experiment II a difference in pitch of 100 Hz between standard and deviant stimuli was used while in experiment I this difference was only 20 Hz (see below for details). This resulted in a more difficult task in experiment I when compared to experiment II.

The auditory selective attention task (see also: Jonkman *et al.*, 1997; Oranje *et al.*, 2000) consisted of 300 stimuli, presented randomly in either the right or the left ear. Two types of stimuli were used: standard tones, which appeared in 80% of the cases, and deviant tones, which appeared in the remaining 20% of the cases. The stimuli were evenly presented to the left or right ear (attended deviants were never presented immediately following each other). The subject was instructed to push a button as fast as possible if the deviant tone occurred in a previously designated ear. Ear designation was balanced randomly across the subjects. After this initial task the subjects were presented the next auditory selective attention task in which they had to monitor the other ear for deviant stimuli. The attribute used to define stimulus type was tone frequency (either 1000 or 1020 Hz in experiment I (l-dopa) and 1000 or 1100 Hz in experiment II (bromocriptine)): the tone frequency defined as standard or deviant was balanced across subjects. The duration of a stimulus (95 dB) was 50 ms, the interstimulus intervals (ISIs) were randomized between 750 and 1000 ms. During the task, the subjects had to maintain their gaze at a fixation cross in the middle of a TV screen.

Signal recording

Electroencephalogram (EEG) recordings were made with an Electrocap (tin electrodes) from 31 scalp locations (10–20 system). However, only data from the electrodes relevant for the present study were analysed (i.e. where the maximum activity for the ERPs measured was to be expected): the midline electrodes Fz and Pz. The left mastoid was used as a reference. Horizontal electro-oculogram (EOG) recordings were made from tin electrodes placed to the outer canthus of each eye. Similarly, vertical EOG was recorded from electrodes placed infra orbital and supra orbital to the left eye. The right eye was used for electro-myography (EMG) measurement of the orbiculus oculi. For all signal recordings a ground electrode was attached to the middle of the forehead. Impedance was kept below 5 k Ω . EEG and EOG signals were recorded with a time constant set to 5 s, EMG signals with a time constant set to 50 ms. All signals were filtered on-line at 40 Hz and were digitized on-line by a computer at a rate of 256 Hz. Sampling started 100 ms before stimulus onset and lasted 1 s.

Signal analysis

Electroencephalogram and EOG data of the selective attention task were analysed using a software package especially designed for EEG and ERP data processing. Firstly, all of the sampled EEG and EOG epochs were baseline corrected and filtered off-line using a 30 Hz, 24 dB/octet digital low-pass filter. Secondly, the EEG was corrected for vertical EOG artefacts by subtracting vertical EOG from EEG epochs by a regression method in the time domain (Kenemans *et al.*, 1991). Lastly, all EEG epochs containing artefacts (saturation of the A/D converter or an amplitude greater than -100 or $100 \mu\text{V}$) were removed from the database. The processing negativity (PN) difference waves were expressed as the ERPs to the attended stimuli, subtracted with the ERPs to

the unattended stimuli, within each channel (i.e. for left and right ear separately). The data for PN was pooled over left and right ears. The P300 amplitude was scored between 300–600 ms and processing negativity between 150–350 ms.

Statistical analysis

The experiments were analysed separately. The P300 amplitudes were analysed by means of planned comparisons using repeated measures ANOVA. The two within factors were: treatment (placebo or l-dopa/bromocriptine), attention (stimulus in attended channel or unattended channel) and stimulus type (standard or deviant). Lead Pz was analysed in the case of the P300. Similarly, repeated measurements ANOVA with within factor treatment was used to analyse the PN data from lead Fz. A repeated measures ANOVA with within factors treatment and performance (hits or false alarms) was used to analyse task performance. Similarly, biochemical (HVA) and endocrine (prolactin) parameters were analysed by means of ANOVA with repeated measurements (within factors time and treatment). Paired samples Student's *t*-tests were used to further explore the significant data as revealed by the ANOVAs.

Results

Endocrinology

Baseline ($t = 0$) plasma levels of prolactin in both experiment I and II did not differ across treatments (l-dopa, bromocriptine or placebo). Both l-dopa and bromocriptine produced a marked decrease in prolactin levels (Fig. 1).

In experiment I, the MANOVA revealed a significant main effect of treatment [$F(1, 14) = 15.63$; $p < 0.001$], time [$F(6,$

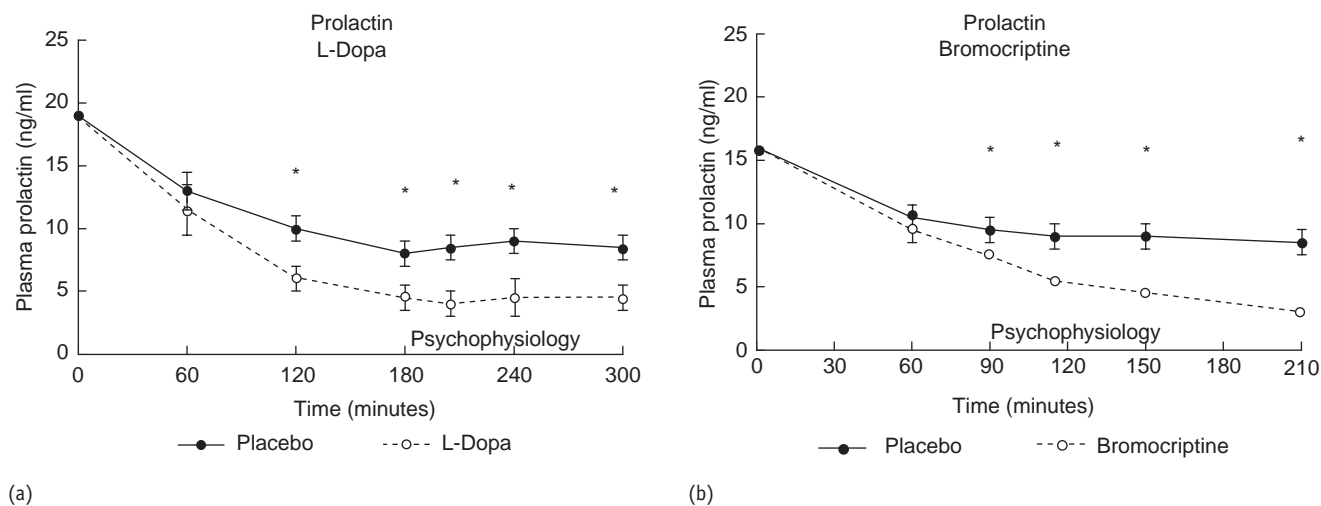


Figure 1 Plasma prolactin levels (\pm SEM) over time in experiment I (l-dopa, (a)) and experiment II (bromocriptine, (b)), for both the placebo and drug treatments, displaying a significant decrease in prolactin level following administration of l-dopa or bromocriptine.

(* = significant difference between placebo and drug treatment, $p < 0.001$)

84) = 27.62; $p < 0.001$) and [treatment \times time] interaction [$F(6, 84) = 5.34$, $p < 0.001$]. Further analysis using Student's *t*-tests revealed a significant reduction in prolactin level from 120 min after oral intake of l-dopa to the end of the test day (Fig. 1a).

Similarly, in experiment II, the MANOVA revealed a significant main effect of treatment [$F(1, 16) = 23.03$; $p < 0.001$], time [$F(5, 80) = 50.38$; $p < 0.001$] and [treatment \times time] interaction [$F(5, 80) = 12.72$; $p < 0.001$]. Bromocriptine significantly decreased plasma prolactin level from the beginning of the psychophysiological assessment ($t = 90$) to the end of the test day (Fig. 1b).

Biochemical measures

Baseline plasma levels of HVA (pHVA) in both experiment I and II did not differ between active and placebo treatment (Fig. 2). In experiment I, l-dopa, the ANOVA revealed a significant main effect of treatment [$F(1, 13) = 142.89$; $p < 0.001$], time [$F(6, 78) = 47.09$; $p < 0.001$] and [treatment \times time] interaction [$F(6, 78) = 51.46$, $p < 0.001$]. Further analysis using Student's *t*-tests revealed a significant increase in pHVA from 60 min after oral intake of the l-dopa capsule to the end of the test day (Fig. 2a). In experiment II no effect of treatment was found (Fig. 2b).

Performance

Three kinds of performance measures were obtained: percentage of hits, percentage of false alarms and mean reaction time to hits. A response was considered a hit when it was given within a window of 200–1000 ms after stimulus presentation. Group means are presented in Table 1. There were significantly more numbers of hits ($t = 4.12$, $p < 0.001$) and false alarms ($t = 3.13$, $p < 0.005$) as well as a significantly increased reaction time ($t = 3.15$,

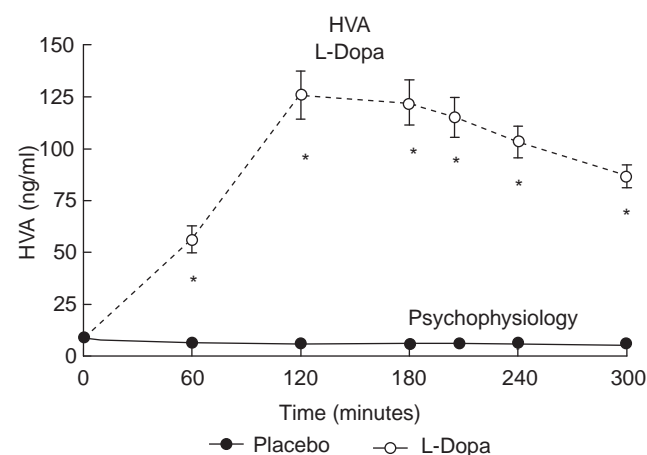
Table 1 Mean performance data of experiment I (l-dopa) and experiment II (bromocriptine), showing a higher percentage of hits and false alarms, as well as an increased reaction time in experiment I compared to experiment II. There were no significant effects of treatment in either experiment (SEM in parentheses).

Treatment	Hits (%)	False alarms (%)	Reaction time (ms)
Experiment I			
placebo	72.9 (4.86)	4.81 (1.31)	514 (4.1)
l-dopa	73.5 (3.87)	5.31 (1.29)	524 (3.6)
Experiment II			
placebo	94.1 (2.06)	0.78 (0.21)	448 (17.1)
bromocriptine	92.3 (2.20)	0.66 (0.25)	453 (18.6)

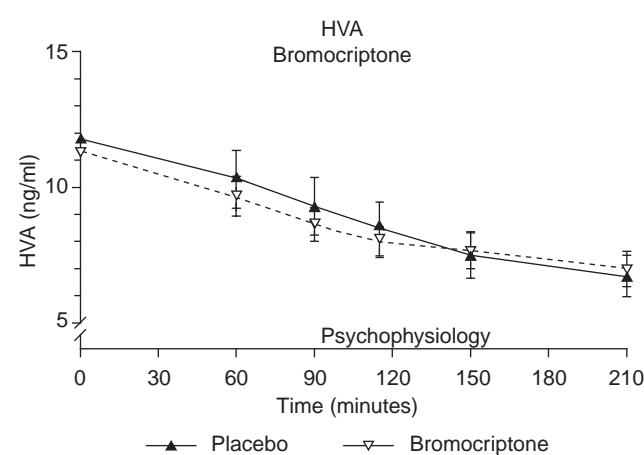
$p < 0.005$) in experiment I, compared to experiment II. No significant effect of treatment (placebo, l-dopa or bromocriptine) was found in either experiment, nor in the subgroups of subjects who became nauseated.

ERP data

P300 Both experiment I and II displayed the same significant differences, irrespective of treatment: an attention main effect (experiment I: [$F(1, 16) = 13.54$; $p < 0.01$], experiment II: [$F(1, 16) = 53.42$; $p < 0.001$]), a stimulus type main effect (experiment I: [$F(1, 16) = 26.13$; $p < 0.001$], experiment II: [$F(1, 16) = 64.27$; $p < 0.001$]) and an attention \times stimulus type interaction effect (experiment I: [$F(1, 16) = 22.77$; $p < 0.001$], experiment II: [$F(1, 16) = 59.36$; $p < 0.001$]) were found. These data indicate a larger P300 amplitude following attended than non-attended stimuli



(a)



(b)

Figure 2 Plasma HVA levels (\pm SEM) in experiment I (l-dopa, (a)) and experiment II (bromocriptine, (b)), for both the placebo and drug treatments, displaying a large increase of plasma HVA following administration of l-dopa, but not bromocriptine, when compared to the placebo treatment.

(* = significant difference between placebo and drug treatment, $p < 0.001$)

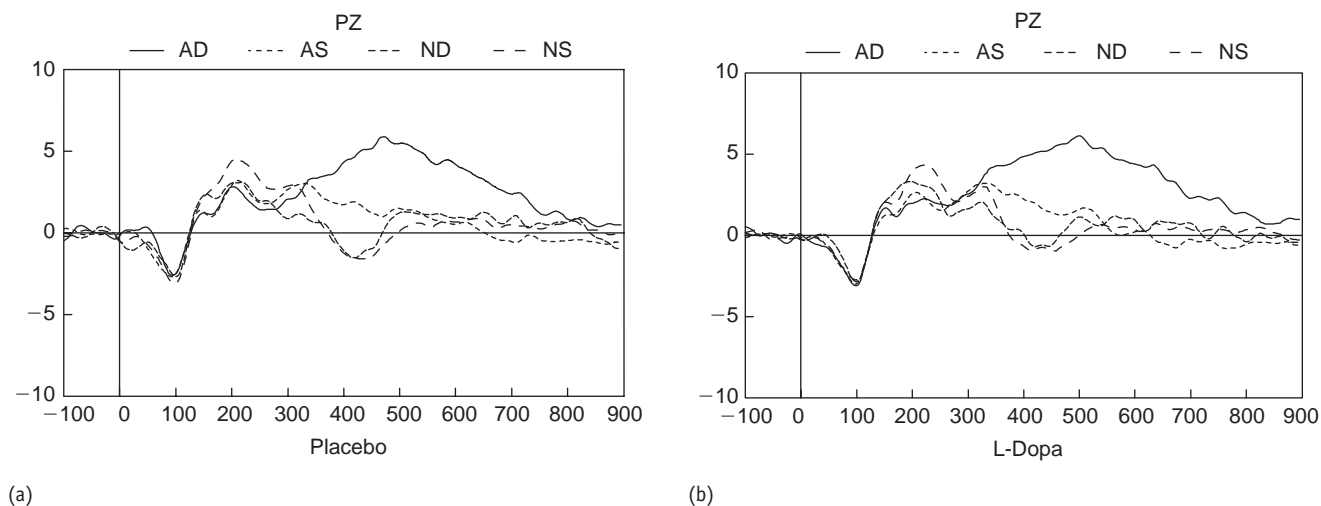


Figure 3a Grand average (average over all subjects) ERPs for lead Pz per treatment for experiment I (l-dopa). There were no significant differences in P300 amplitude between the placebo and l-dopa treatment.

(AD = attended deviant; AS = attended standard; ND = non-attended deviant; NS = non-attended standard)

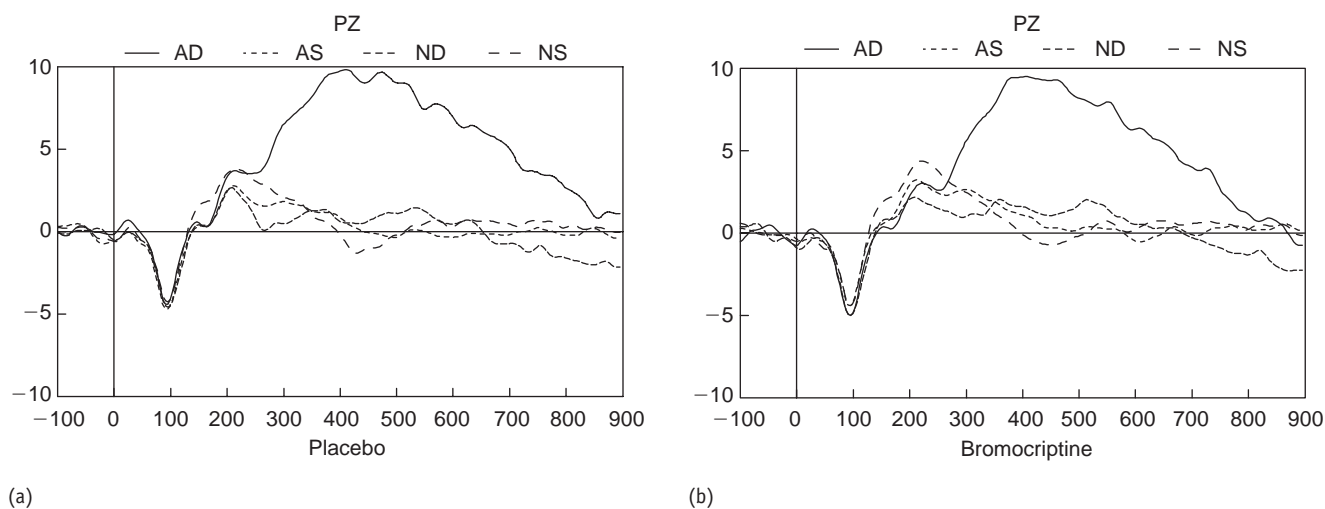


Figure 3b Grand average ERPs for lead Pz per treatment for experiment II (bromocriptine). There were no significant differences in P300 amplitude between the placebo and bromocriptine treatment.

(AD = attended deviant; AS = attended standard; ND = non-attended deviant; NS = non-attended standard)

(attention main effect) and a larger amplitude following deviant stimuli than standard stimuli (stimulus type main effect), while a larger amplitude following deviant stimuli was found than following standard stimuli (attention \times stimulus type interaction). The P300 amplitude to targets were significantly more pronounced in experiment II than in experiment I ($t = 3.08, p < 0.005$). No significant effect of treatment was found in either experiment, nor in the subgroups of subjects who became nauseated (Figs 3a and b).

Processing negativity In both experiments PN (experiment I: [$F(1, 16) = 96.01; p < 0.001$], experiment II: [$F(1, 16) = 99.87; p < 0.001$]) was found (expressed as a difference from zero), irrespective of treatment, indicating enhanced processing activity to stimuli in the attended channel. Similar to the P300 data, no significant effect of treatment was found in either experiment, nor in the subgroups of subjects who became nauseated (Fig. 4).

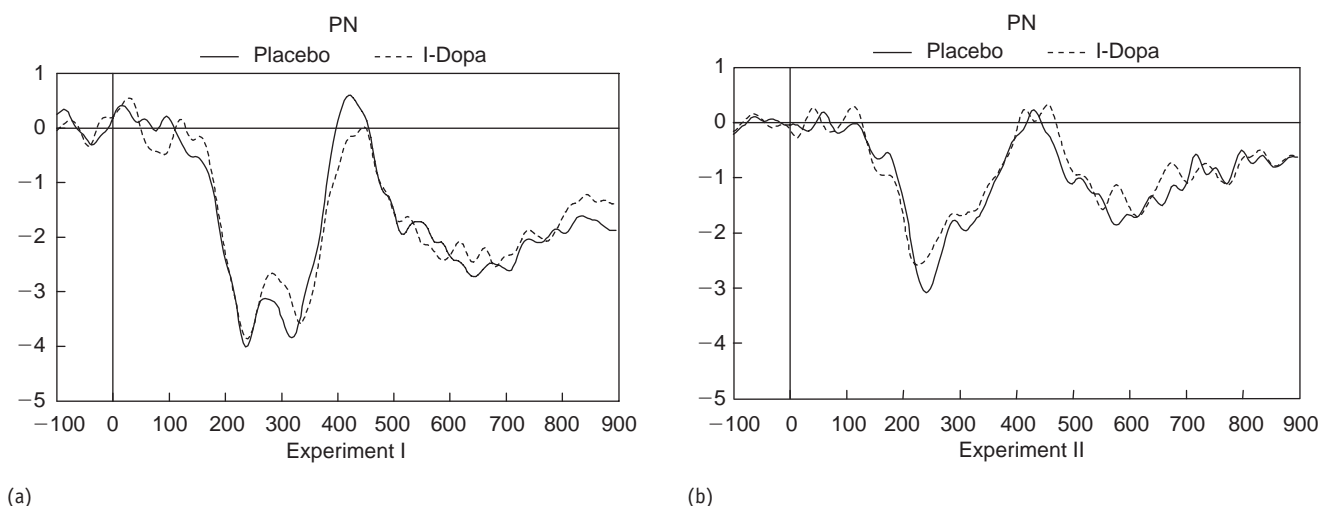


Figure 4 Grand average difference waves (lead Fz) for processing negativity, for study I (l-dopa) and experiment II (bromocriptine). In both experiments there were no significant differences found between placebo and active treatment.

Discussion The effect of increased central dopaminergic activity on two psychophysiological parameters of selective attention (P300 amplitude and processing negativity (PN)) was investigated in healthy volunteers. In two separate experiments, central dopaminergic activity of healthy volunteers was increased by means of either a dose of 300 mg l-dopa (a precursor of dopamine) or a dose of 1.25 mg bromocriptine (a D2-receptor agonist), after which the subjects were tested in a dichotic selective attention paradigm (auditory oddball task). For this kind of task usual attention related phenomena on P300 amplitude were found, i.e. an increase in amplitude following deviant stimuli compared to standard stimuli and following attended stimuli compared to unattended stimuli, irrespective of treatment. Effects were largest to task relevant targets. No effect of treatment was found on the P300 amplitude. Similarly, PN was found regardless of treatment, while no effect of treatment was found. Furthermore, on a more behavioural level, no treatment effects were found on task performance, i.e. reaction time, number of hits and false alarms.

Limited data are available on the neurotransmitters that modulate PN. In a dichotic oddball task, droperidol (an anaesthetic with high affinity for dopamine receptors, and weaker for adrenergic receptors) led to a near significant reduction of early (200–400 ms) PN (Shelley *et al.*, 1997). In another study of selective attention, haloperidol (D2 antagonist) was found to decrease middle latency (300–500 ms) PN only, without affecting early (100–300 ms) or late (500–700 ms) latency PN at Fz (Kahkonen *et al.*, 2001). This suggests that the mild disruptive effect of droperidol on PN (Shelley *et al.*, 1997) might be explained by its antagonistic action on the dopaminergic system or by its analgesic qualities, but not by its antagonistic effect on the noradrenergic system. This would agree with the study of Mervaala *et al.* (1993) in which no effect was found of the α -2 antagonist atipamezole (ATI) on PN, indicating no effect of increased noradrenergic activity on PN, although the group size ($n = 6$) was rather small. Similarly, serotonin seems

to have no influence on PN (Ahveninen *et al.*, 2003). Summarized, there seems to be little evidence for a noradrenergic or serotonergic modulation of (early) PN, while evidence for a dopaminergic modulation is restricted to droperidol, a compound that has not only affinity for the dopaminergic system, but also has analgesic qualities and affinity for the noradrenergic system. However, the results of the current study do not support a dopaminergic modulation of PN. This makes it likely that something other than the dopaminergic, serotonergic or noradrenergic system, modulates PN. Indeed, we recently found that a sub-anaesthetic dose of ketamine reduces early (150–350 ms) PN (Oranje *et al.*, 2000; Oranje *et al.*, submitted) in healthy volunteers, which is consistent with a glutamatergic modulation of PN. The disruptive effect of droperidol on PN (Clark *et al.*, 1987; Shelley *et al.*, 1997) could then be explained by its analgesic qualities, rather than its antagonistic effect on the dopaminergic system. A glutamatergic modulation of PN would also explain why schizophrenic patients, in spite of treatment with typical antipsychotics, which have little or no affinity for the glutamatergic system, still show impaired selective attention (e.g. Baribeau-Braun *et al.*, 1983; Iwanami *et al.*, 1998; Strandburg *et al.*, 1999).

In the present study, an increase in P300 amplitude was found following deviant stimuli compared to standard stimuli and following attended stimuli compared to unattended stimuli, irrespective of treatment. This is consistent with studies in which similar selective attention paradigms were used (e.g. Baribeau-Braun *et al.*, 1983; Ward *et al.*, 1991; Oranje *et al.*, 2000). However, neither l-dopa nor bromocriptine affected P300 amplitude in the present study. This result suggests that the P300 amplitude is not modulated by dopaminergic activity, which is in line with the study of Luthringer *et al.* (1999), in which no effects of apomorphine (D2/D3 agonist) on P300 topography (P300 amplitude was not investigated) in healthy male volunteers was found. A more complex interaction between the dopaminergic system and

P300 amplitude was found in the study of Takeshita and Ogura (1994) in which sulpiride (D2 antagonist) increased P300 amplitude in an initial low P300 amplitude subgroup of healthy volunteers, while it decreased the P300 in the initially high P300 amplitude group, although on the group as a whole no effects on P300 amplitude were found, indicating a relationship between dopamine antagonists and P300 amplitude that follows the law of initial value. Similarly, in a follow-up study, they found a trend for bromocriptine (D2 agonist) to reduce the P300 amplitude at electrode Cz (normally the highest activity for the P300 amplitude is found at electrode Pz) of the subgroup of healthy volunteers that showed initial high P300 amplitudes at that electrode.

A reduced P300 amplitude is most consistently found in patients with schizophrenia (e.g. Roth and Cannon, 1972; Baribeau-Braun *et al.*, 1983; Boutros *et al.*, 1997; Karoumi *et al.*, 2000; Jeon and Polich, 2003; for a review: Friedman, 1991). Furthermore, Coburn *et al.* (1998) found a decreased amplitude and an increased latency of the P300 in unmedicated patients with schizophrenia when compared to healthy control subjects. Following a 6-week treatment period with remoxipride or haloperidol (both D2-receptor antagonists) they found a normalized P300 latency but still a decreased P300 amplitude. In addition, Oishi *et al.* (1996) found no effects of a dose of 50 mg l-dopa (i.v.) on the P300 amplitude in patients with Parkinson's disease. Summarized, the results of the present study, together with the results from earlier studies with healthy volunteers and more clinically-related studies, point towards little or no evidence for a dopaminergic modulation of P300 amplitude. Evidence for the involvement of systems other than the dopaminergic system in the modulation of the P300 is found in the study of Umbricht *et al.* (1998): they reported an increased P300 amplitude in patients with schizophrenia following a switch in treatment from haloperidol to treatment with clozapine. Clozapine displays only weak affinity for dopaminergic (D1 and D2) receptor sites and relatively strong affinity for adrenergic ($\alpha 1$ and $\alpha 2$), serotonin (5-HT_{2a}) and histamine (H1) receptor sites, while haloperidol is a potent and relatively selective D2-receptor antagonist (Tandon *et al.*, 1999). Furthermore, using the same design as that of the present study, we (Oranje *et al.*, 2000) found that a sub-anaesthetic dose of ketamine reduced the P300 amplitude and PN of healthy volunteers, a result that we replicated recently in a follow-up study (Oranje *et al.*, submitted). These studies suggest an involvement of the glutamatergic system instead of the currently investigated dopaminergic system in the modulation of the P300 amplitude, which agrees with the conclusions of Frodl Bauch *et al.* (1999a) in their review on the neurochemical substrates of the P300.

The inability of l-dopa and bromocriptine to affect the parameters of selective attention in healthy subjects as found in the present study, cannot be explained by the dosages being too low: both l-dopa and bromocriptine significantly reduced plasma prolactin concentration, and l-dopa significantly increased plasma HVA concentration, which are both indicators of an increased central dopaminergic activity. Furthermore, the dose of l-dopa administered in the present study, 300 mg, falls well within the therapeutic range of dosages in the treatment of Parkinson's disease (varying from 150 and 1500 mg) (Munson *et al.*, 1995),

while a dose of 1.25 mg bromocriptine (which is half of the dose as used in the current study) was, for instance, effective in reducing sensory gating in healthy subjects in two studies (Abduljawad *et al.*, 1998; Abduljawad *et al.*, 1999). Another argument could be that the selective attention paradigm that was used in the current study was too easy to leave room for improvement by, for instance, an increase in prefrontal dopaminergic transmission (in the case of l-dopa). However, a more difficult version of the selective attention task was used in the l-dopa condition, which is reflected in a lower percentage of hits and a lower P300 amplitude to targets, leaving ample room for improvement. Therefore, the results are best explained in terms of the pharmacological ineffectiveness of dopamine agonists on the parameters that were assessed in the present study.

In summary, neither l-dopa nor bromocriptine was found to affect task performance, processing negativity or P300 amplitude in healthy volunteers, phenomena that are usually disrupted in patients with schizophrenia. This indicates that P300 amplitude and PN are neither affected by a global (l-dopa) increased dopaminergic activity, nor by a more selectively towards striatal areas targeted (bromocriptine) increase in dopaminergic activity. Future research should focus on the involvement of other neurotransmitter systems in these electrophysiological parameters of selective attention (e.g. the glutamatergic system).

References

- Abduljawad K A, Langley R W, Bradshaw C M, Szabadi E (1998) Effects of bromocriptine and haloperidol on prepulse inhibition of the acoustic startle response in man. *J Psychopharmacol* 12: 239–245
- Abduljawad K A, Langley R W, Bradshaw C M, Szabadi E (1999) Effects of bromocriptine and haloperidol on prepulse inhibition: comparison of the acoustic startle eyeblink response and the N1/P2 auditory-evoked response in man. *J Psychopharmacol* 13: 3–9
- Ahveninen J, Jaaskelainen I P, Pennanen S, Liesivuori J, Ilmoniemi R J, Kahkonen S (2003) Auditory selective attention modulated by tryptophan depletion in humans. *Neurosci Lett* 340: 181–184
- Andreasen N C, Flaum M, Arndt S (1992) The comprehensive assessment of symptoms and history (CASH): an instrument for assessing psychopathology and diagnosis. *Arch Gen Psychiatry* 49: 615–623
- Antal A, Keri S, Bodis-Wollner I (1997) Dopamine D2 receptor blockade alters the primary and cognitive components of visual evoked potentials in the monkey, *Macaca fascicularis*. *Neurosci Lett* 232: 179–181
- Baribeau-Braun J, Picton T W, Gosselin J Y (1983) Schizophrenia: a neurophysiological evaluation of abnormal information processing. *Science* 219: 874–876
- Boutros N N, Nasrallah H, Leighty R, Torello M (1997) Auditory evoked potentials, clinical vs research applications. *Psychiatry Res* 69: 183–195
- Cedarbaum J M, Kutt H, McDowell F H (1989) A pharmacokinetic and pharmacodynamic comparison of Sinemet CR (50/200) and standard Sinemet (25/100). *Neurology* 39: 38–44
- Clark C R, Geffen G M, Geffen L B (1987) Catecholamines and attention: II. Pharmacological studies in normal humans. *Neurosci Biobehav Rev* 11: 353–364
- Coburn K L, Shillcutt S D, Tucker K A, Estes K M, Brin F B, Merai P, Moore N C (1998) P300 delay and attenuation in schizophrenia: reversal by neuroleptic medication. *Biol Psychiatry* 44: 466–474
- del Pozo E, Schluter K, Nuesch E, Rosenthaler J, Kerp L (1986) Pharmacokinetics of a long-acting bromocriptine preparation (Parlodel LA)

- and its effect on release of prolactin and growth hormone. *Eur J Clin Pharmacol* 29: 615–618
- Dempski R E, Scholtz E C, Oberholtzer E R, Yeh K C (1989) Pharmaceutical design and development of a Sinemet controlled-release formulation. *Neurology* 39: 20–24
- Drewe J, Mazer N, Abisch E, Krummen K, Keck M (1988) Differential effect of food on kinetics of bromocriptine in a modified release capsule and a conventional formulation. *Eur J Clin Pharmacol* 35: 535–541
- Duncan G E, Sheitman B B, Lieberman J A (1999) An integrated view of pathophysiological models of schizophrenia. *Brain Res Brain Res Rev* 29: 250–264
- Endicott J, Spitzer R L (1978) A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 35: 837–844
- Frazer A E, Molinoff P B E, Winokur A E (1994) *Biological Bases of Brain Function and Disease*. Raven Press, New York, NY
- Friedman D (1991) Endogenous scalp-recorded brain potentials in schizophrenia: a methodological review. In Steinhauer S R, Gruzeliel J H, Zubin J (eds), *Neuropsychology, Psychophysiology, and Information Processing*. Elsevier Science Publishing Co., Amsterdam, pp. 91–127
- Frodl Bauch T, Bottlender R, Hegerl U (1999a) Neurochemical substrates and neuroanatomical generators of the event-related P300. *Neuropsychobiology* 40: 86–94
- Frodl Bauch T, Gallinat J, Meisenzahl E M, Moller H J, Hegerl U (1999b) P300 subcomponents reflect different aspects of psychopathology in schizophrenia. *Biol Psychiatry* 45: 116–126
- Green M F (1998) *Schizophrenia from a Neurocognitive Perspective: Probing the Impenetrable Darkness*. Allyn and Bacon, Inc., Boston, MA, pp. xii, 190
- Iwanami A, Isono H, Okajima Y, Noda Y, Kamijima K (1998) Event-related potentials during a selective attention task with short interstimulus intervals in patients with schizophrenia. *J Psychiatry Neurosci* 23: 45–50
- Javitt D C, Doneshka P, Grochowski S, Ritter W (1995) Impaired mismatch negativity generation reflects widespread dysfunction of working memory in schizophrenia. *Arch Gen Psychiatry* 52: 550–558
- Jeon Y W, Polich J (2003) Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. *Psychophysiology* 40: 684–701
- Jonkman L M, Kemner C, Verbaten M N, Koelega H S, Camfferman G, Gaag R J v d, Buitelaar J K, van Engeland H (1997) Event-related potentials and performance of Attention-Deficit Hyperactivity Disorder: children and normal controls in auditory and visual selective attention tasks. *Biol Psychiatry* 41: 595–611
- Juckel G, Mullerschubert A, Gaebel W, Hegerl U (1996) Residual symptoms and P300 in schizophrenic outpatients. *Psychiatry Res* 65: 23–32
- Kahkonen S, Ahveninen J, Jaaskelainen I P, Kaakkola S, Näätänen R, Hutunnen J, Pekkonen E (2001) Effects of haloperidol on selective attention: a combined whole-head MEG and high-resolution EEG study. *Neuropsychopharmacology* 25: 498–504
- Kahn R S, Davidson M (1995) Dopamine in schizophrenia. In den Boer J A, Westenberg H G M, van Praag H M (eds), *Advances in the Neurobiology of Schizophrenia*: Wiley & Sons Ltd, New York, pp. 204–220
- Karoumi B, Laurent A, Rosenfeld F, Rochet T, Brunon A M, Dalery J (2000) Alteration of event related potentials in siblings discordant for schizophrenia. *Schizophr Res* 41: 325–334
- Kayser J, Bruder G E, Tenke C E, Stuart B K, Amador X F, Gorman J M (2001) Event-related brain potentials (ERPs) in schizophrenia for tonal and phonetic oddball tasks. *Biol Psychiatry* 49: 832–847
- Kenemans J L, Molenaar P C, Verbaten M N, Slangen J L (1991) Removal of the ocular artifact from the EEG: a comparison of time and frequency domain methods with simulated and real data. *Psychophysiology* 28: 114–121
- Kopitar Z, Vrhovac B, Povsic L, Plavsic F, Francetic I, Urbancic J (1991) The effect of food and metoclopramide on the pharmacokinetics and side effects of bromocriptine. *Eur J Drug Metab Pharmacokinet* 16: 177–181
- Kraepelin E (1913) *Psychiatrie, ein Lehrbuch für Studierende und Ärzte*, 8th edn. Barth, J.A., Leipzig
- Kruk Z L, Pycock C J (1991) *Neurotransmitters and drugs*, 3rd ed. Chapman and Hall, London
- Laruelle M, Kegeles L S, Abi-Dargham A (2003) Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Annals New York Academy of Sciences* 1003: 138–158
- LeWitt P A, Nelson M V, Berchou R C, Galloway M P, Kesaree N, Kareti D, Schlick P (1989) Controlled-release carbidopa/levodopa (Sinemet 50/200 CR4): clinical and pharmacokinetic studies. *Neurology* 39: 45–53
- Luthringer R, Rinaudo G, Toussaint M, Bailey P, Muller G, Muzet A, Macher J (1999) Electroencephalographic characterization of brain dopaminergic stimulation by apomorphine in healthy volunteers. *Neuropsychobiology* 39: 49–56
- McGhie A, Chapman J (1961) Disorders of attention and perception in early schizophrenia. *Brit J Med Psychol* 34: 103–116
- McKetin R, Ward P B, Catts S V, Mattick R P, Bell J R (1999) Changes in auditory selective attention and event-related potentials following oral administration of D-amphetamine in humans. *Neuropsychopharmacology* 21: 380–390
- Mervaaala E, Alhainen K, Helkala E L, Partanen J, Jousmaki V, Vayrynen M, Heinonen E, Riekkinen P (1993) Electrophysiological and neuropsychological effects of a central alpha 2-antagonist atipamezole in healthy volunteers. *Behav Brain Res* 55: 85–91
- Michie P T, Fox A M, Ward P B, Catts S V, Mcconaghy N (1990) Event-related potential indices of selective attention and cortical lateralization in schizophrenia. *Psychophysiology* 27: 209–227
- Muller T J, Kalus P, Strik W K (2001) The neurophysiological meaning of auditory P300 in subtypes of schizophrenia. *World J Biol Psychiatry* 2: 9–17
- Munson P L, Mueller R A, Breese G R (1995) *Principles of Pharmacology, Basic Concepts and Clinical Applications*. Chapman and Hall, New York
- Näätänen R (1990) The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behav Brain Sci* 13: 201–288
- Nieoullon A (2002) Dopamine and the regulation of cognition and attention. *Prog Neurobiol* 67: 53–83
- Nishimura N, Ogura C, Ohta I (1995) Effects of the dopamine-related drug bromocriptine on event-related potentials and its relation to the law of initial value. *Psychiatry Clin Neurosci* 49: 79–86
- Oishi M, Mochizuki Y, Hara M, Du C M, Takasu T (1996) Effects of intravenous L-dopa on P300 and regional cerebral blood flow in parkinsonism. *Int J Neurosci* 85: 147–154
- Oranje B, Gispen-de Wied C C, Verbaten M N, Kahn R S (submitted) The effects of ketamine and haloperidol on human selective attention
- Oranje B, Gispen-de Wied C C, Verbaten M N, Kahn R S (2004) Increasing dopaminergic activity in humans: effects of l-dopa and bromocriptine on human sensory gating. *J Psychopharmacol* 18: 388–394
- Oranje B, van Berckel B N M, Kemner C, van Ree J M, Kahn R S, Verbaten M N (2000) The effects of a sub-anaesthetic dose of ketamine on human selective attention. *Neuropsychopharmacology* 22: 293–302
- Robertson D R, Higginson I, Macklin B S, Renwick A G, Waller D G,

- George C F (1991) The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. *Br J Clin Pharmacol* 31: 413–417
- Roth W T, Cannon E H (1972) Some features of the auditory evoked response in schizophrenics. *Arch Gen Psychiatry* 27: 466–471
- Sevostianov A, Fromm S, Nechaev V, Horwitz B, Braun A (2002) Effect of attention on central auditory processing: an fMRI study. *Int J Neurosci* 112: 587–606
- Shelley A M, Catts S V, Ward P B, Andrews S, Mitchell P, Michie P, Mcconaghy N (1997) The effect of decreased catecholamine transmission on ERP indices of selective attention. *Neuropsychopharmacology* 16: 202–210
- Shutara Y, Koga Y, Fujita K, Takeuchi H, Mochida M, Takemasa K (1996) An event-related potential study on the impairment of automatic processing of auditory input in schizophrenia. *Brain Topogr* 8: 285–289
- Strandburg R J, Marsh J T, Brown W S, Asarnow R F, Guthrie D, Harper R, Nuechterlein K H (1999) Continuous-processing related ERPs in adult schizophrenia: continuity with childhood onset schizophrenia. *Biol Psychiatry* 45: 1356–1369
- Strik W K, Dierks T, Kulke H, Maurer K, Fallgatter A (1996) The predictive value of P300-amplitudes in the course of schizophrenic disorders. *J Neural Transm* 103: 1351–1359
- Takeshita S, Ogura C (1994) Effect of the dopamine D2 antagonist sulpiride on event-related potentials and its relation to the law of initial value. *Int J Psychophysiol* 16: 99–106
- Tandon R, Milner K, Jibson M D (1999) Antipsychotics from theory to practice: integrating clinical and basic data. *J Clin Psychiatry* 60 (Suppl. 8): 21–28
- Umbricht D, Javitt D, Novak G, Bates J, Pollack S, Lieberman J, Kane J (1998) Effects of clozapine on auditory event-related potentials in schizophrenia. *Biol Psychiatry* 44: 716–725
- Ward P B, Catts S V, Fox A M, Michie P T, Mcconaghy N (1991) Auditory selective attention and event-related potentials in schizophrenia. *Br J Psychiatry* 158: 534–539
- Woods D L (1990) The physiological basis of selective attention: implications of event-related potential studies. In Rohrbaugh J W, Parasuraman R, Johnson R Jr (eds), *Event-related Brain Potentials: Basic Issues and Applications*. Oxford University Press, New York, pp. 178–209
- Yeh K C, August T F, Bush D F, Lasseter K C, Musson D G, Schwartz S, Smith M E, Titus D C (1989) Pharmacokinetics and bioavailability of Sinemet CR: a summary of human studies. *Neurology* 39: 25–38