Psychopharmacology (1999) 145:123–132

ORIGINAL INVESTIGATION

S. Kröner · U. Schall · P.B. Ward · G. Sticht
M. Banger · H.-T. Haffner · S.V. Catts

Effects of prepulses and *d*-amphetamine on performance and event-related potential measures on an auditory discrimination task

Received: 30 March 1998 / Final version: 10 February 1999

Abstract *Rationale:* Prepulse inhibition (PPI) of the startle reflex is a measure of sensorimotor gating, that is the processing of the startle stimulus (S2) is inhibited by the interfering processing of a closely preceding prepulse (S1). It has been demonstrated that PPI is disrupted in a variety of mental disorders and that several neurotransmitter systems, including dopamine, participate in the modulation of sensorimotor gating. Previous studies have also shown that a task-relevant S1 enhances PPI in healthy subjects but not in schizophrenic patients. These findings indicate an influence of attentional processes on sensorimotor gating and an impairment of this modulation in schizophrenia. *Objective:* Assuming a dopamine-mediated suppression of S1 processing as a mechanism of resource management and selective attention, which might be impaired in certain mental disorders, the present study investigated the effects of the indirect dopaminergic agonist *d*-amphetamine on prepulse-altered S2 discrimination and event related potentials (ERPs). *Methods:* Twelve healthy volunteers were tested in a double-blind, placebo-controlled experimental design. Here, S2 is the target in a difficult Go/NoGo auditory discrimination task. *Results:* Confirming our previous results, S2 processing is "accentuated" by a weak acoustic prepulse in healthy subjects, thus leading to a lower rate of errors of omission but also to more false alarms (i.e. a liberal response bias). This performance change correlated with a prepulse-induced increase in the amplitude of the P3 ERP towards non-targets ("prepulse-induced non-target positivity"; PINTP). In addition, the results of the present study show that under prepulse conditions amphetamine disrupts "S2 accentuation" associated with a dose-related reduction of the P2 component of the S1 response and a plasma level related reduction of PINTP. *Conclusions:* These data suggest an involuntary attentional shift towards S1 processing with increasing dopamine-release similar to that observed in patients with schizophrenia or OCD. It is concluded that sensory gating alters selective attention via dopaminergic modulation.

Key words Prepulse inhibition · Sensorimotor gating · Auditory discrimination task · Go/NoGo procedure · Selective attention · *d*-Amphetamine · Dopamine · Schizophrenia

S. Kröner
The University of Bochum, Department for Biopsychology, Bochum, Germany

U. Schall (✉)
Discipline of Psychiatry, Faculty of Medicine and Health Sciences, The University of Newcastle, Callaghan NSW 2308, Australia
e-mail: ulrich.schall@uni-essen.de
Fax: +61-2-4924-6608

M. Banger
University of Essen, Clinic for General Psychiatry, Virchowstrasse 174, D-45147 Essen, Germany

P.B. Ward · S.V. Catts
The University of New South Wales, School of Psychiatry, Schizophrenia Research Unit, Sydney, Australia

G. Sticht
The University of Cologne, Institute for Forensic Medicine, Köln, Germany

H.-T. Haffner
The University of Essen, Institute for Forensic Medicine, Essen, Germany

Introduction

The P3 event-related potential (ERP) has been widely used to investigate cognitive mechanisms of information processing and information processing deficits in a variety of pathological groups. Topographic recordings under different experimental conditions led to the conclusion that the P3 component comprises contributions from a variety of source generators dependent on the type of information being processed (Ruchkin et al. 1990; Johnson 1993). In oddball paradigms, for instance, P3 appears as two distinct, context-dependent wave forms: P3a is elicited by unexpected events (or novel stimuli) with a frontal maximum while P3b has a parietal maximum when it is elicited by active stimulus processing (i.e. in auditory or visual discrimination tasks; Squires et al. 1975a). P3a and P3b can also be distinguished by dif-

ferent latencies, of approximately 240 and 350 ms post-stimulus onset, respectively (Squires et al. 1975a). Therefore, it has been concluded that P3a amplitude is an index of attention being directed towards the stimulus or source of stimulation (Ford et al. 1976) whereas P3b amplitude provides an index of decision confidence and signal probability, thus reflecting two major elements of the signal detection paradigm (Squires et al. 1975a,b; Campbell et al. 1979).

In line with these scalp-recorded data, two distinct P3 potentials, one with a generator source in the medial temporal lobe and one in the frontal lobe, were identified by intracranial recordings (McCarthy and Wood 1987; Kiss et al. 1989; Smith et al. 1990; Baudena et al. 1995; Halgren et al. 1995). However, relatively small lesions of the posterior superior temporal plane diminish both P3a *and* P3b amplitudes, indicating that the auditory association cortex in the temporo-parietal junction is important for generation of both P3 components (Knight et al. 1989; Verleger et al. 1994). Prefrontal lesions involving fronto-limbic pathways are associated with a *reduction* of P3a amplitude (Knight 1984), whilst patients with unilateral prefrontal lesions show *enhanced* P3 amplitudes to deviant non-target (NT) stimuli while target-(T)-evoked P3b amplitudes are not affected (Nasman and Dorio 1993). The authors concluded that the prefrontal contribution to P3b is attention related.

These data suggest that P3a and P3b are generated in partly overlapping neural networks involved in the *selective* processing of information, a feature often impaired in patients with frontal ablation (Milner and Petrides 1984). The ERP paradigm used in the present study builds upon previous findings suggesting that the P3a component shares some characteristics with the myogenic startle response [i.e. prepulse inhibition (PPI); Sugawara et al. 1994] similar to the inhibition of the N1 component upon immediately preceding acoustic pulses (Putnam and Roth 1990; Perlstein et al. 1993). However, in contrast to the P3b component, no difference of the relative PPI of N1 between diagnostic groups was found [i.e. patients with obsessive-compulsive disorder (OCD) or schizophrenia versus healthy subjects; Schall et al. 1996, 1997]. Since P3a amplitude and startle eye-blink measures also have both been found to be significantly correlated with frontal grey matter volumes (Ford et al. 1994), it is concluded that attenuation of P3a (and "frontal" P3b) amplitude may provide an index of frontal brain dysfunction, analogous to deficits of sensorimotor gating of the startle reflex (Braff et al. 1992).

Frontal lobe impairment has been associated with impaired performance on delayed alternation tasks, particularly withholding a response in Go/NoGo procedures (Warren and Akert 1964; Drewe 1975; Verin et al. 1993). In such tasks non-target (or NoGo) P3s differed significantly from target (or Go) P3s. NT-P3s had a later onset and a more frontal scalp distribution whilst T-P3s were maximal at parietal electrode sites and were of smaller amplitude than the frontal NT-P3s (Hillyard et al. 1976; Simson et al. 1977; Pfefferbaum et al. 1985; Schupp et al. 1994). Increased task difficulty was also associated with a trend towards smaller NT-P3 amplitudes (Pfefferbaum et al. 1985). Schupp and colleagues (1994) also found reduced startle reflex magnitude in the NoGo condition which was significantly correlated with increased P3 positivity.

Further evidence for a common frontal mechanism for NT-P3 positivity and startle inhibition derived from PPI studies in an auditory Go/NoGo discrimination task: Schall and Ward (1996) showed that a prepulse with a 100-ms lead interval changed the ratio of the P3 waves in response to target or non-target stimuli, respectively. This effect was maximal at the frontal midline electrode (Fz) and resulted mainly from an increase of the P3 amplitude evoked by non-target stimuli. This "prepulse-induced non-target positivity" (PINTP) was significantly associated with the response bias (β) across different pre- and postpulse conditions and let particularly in the 100-ms prepulse condition to a change towards a liberal response bias due to a higher rate of false alarms (Schall and Ward 1996). By contrast, in schizophrenic patients the perceptual sensitivity was decreased due to increased errors of omission along with a small PINTP (Schall et al. 1996) suggestive of a common frontal neural mechanism that mediates PINTP and sensory (-motor) gating.

The present study investigated the pharmacological action of the non-specific dopamine agonist *d*-amphetamine on PINTP and performance in healthy volunteers using an auditory Go/NoGo discrimination task with and without task-irrelevant prepulse stimuli. The experiment builds on the procedure developed by Schall and Ward (1996). During three sessions – one control and two drug conditions, to which healthy volunteers were assigned randomly under double-blind conditions – subjects were asked to listen to a series of two tones and to respond only to the target tone. Target and non-target tones were presented under three conditions with equal probabilities, either without any prepulse, or with prepulses that lead with 100 ms or 500 ms, respectively. In addition, within each session the task difficulty increased over three otherwise identical blocks. The subjects' event related potentials (ERPs) and behavioural parameters were recorded and the effects of prepulses and amphetamine on PINTP and response bias were measured.

Animal studies have demonstrated that presynaptic dopamine-glutamate interactions in the nucleus accumbens regulate sensorimotor gating (Wan et al. 1995). Via this mechanism, startle PPI is disrupted dose-dependently by dopamine agonists (Mansbach et al. 1988; Peng et al. 1990). It can be reversed by dopamine antagonists (Swerdlow et al. 1991, 1994). Furthermore, an intact frontal dopaminergic systems seems to be crucial for the normal functioning of gating mechanisms (Swerdlow et al. 1995a). Thus, assuming a dopaminergic modulation of sensory gating, it was postulated that there would be a dose-dependent decrease of PINTP associated with a more conservative response bias in the 100-ms prepulse condition when d-amphetamine was administered to healthy subjects similar to that found in psychotic patients (Schall et al. 1996; Bender et al. 1999).

Materials and methods

Subjects

Twelve healthy subjects [students and staff of the University of New South Wales and the South Eastern Sydney Area Health Service, four women and eight men with a median age of 26 years (range 20–35 years)], who met the following inclusion criteria, participated in this study. Subjects were between 18 and 35 years of age, with a body weight between 45 kg and 90 kg or body mass index (BMI) range of 18–27, no current or previous history of hypertension, attention deficit hyperactivity disorder, DSM-IV axis I psychiatric disorder, no family history of mania or schizophrenia in first degree relatives and no current or previous DSM-IV diagnosis of drug or alcohol dependence as assessed by a computerized version of the Structured Clinical Interview (SCID; Spitzer et al. 1990), Subjects with diseases of the nervous system or other medical problems that would interfere with the measures to be obtained in the course of the study were also excluded. Written informed consent was obtained and subjects received a small honorarium for participation in the experiment. The study protocol was approved by the Research Ethics Committee of the South Eastern Sydney Area Health Service.

Stimulus parameters

Auditory stimuli were generated using the NeuroScan Stim System (NeuroScan, Inc.). They were presented against a white noise background (30 dB SPL) and delivered through headphones. Four tones (65 dB SPL) each of 50 ms duration (including 10 ms rise/fall time) served as the target and non-target stimuli which subjects were required to discriminate. The target was always a 1-kHz tone which was presented along with one of three non-target tones with a probability of P=0.5 in six blocks of 90 tones. The three different NT tones were presented in order of increasing discrimination difficulty: NT frequency in block 1 and 2 was 965 Hz, in block 3 and 4 975 Hz, and in block 5 and 6 985 Hz. Within each block, the T and NT tones were presented equiprobably with either no prepulse or a prepulse (1.8 V/0.6 ms rectangular click) 100 ms or 500 ms prior to the T and NT tones. The latency window for valid target responses was set to 100–1500 ms post-S2.

Event-related potential (ERP) recording

Fifteen channels of EEG were recorded from midline (Fpz, Fz, Cz, and Pz) and lateral (F7, F8, T3, T4, T5, and T6; international 10–20 system; Electrocap International) scalp electrodes and from the left and right mastoid with a nose reference (all impedances <10 kΩ). Results obtained from analysis of the midline electrodes are reported here. The EEG was amplified (Grass Model 12 Neurodata ×20 000) and bandpass filtered between 0.01 and 30 Hz. ERPs were averaged (NeuroScan software; NeuroScan Inc.) over epochs of 1400 ms relative to a baseline 200 ms prior to the onset of the initial stimulus for each trial (prepulse or tone, dependent on condition). Trials in which the vertical or the horizontal EOG exceeded 50 μV were excluded from averaging. ERPs were averaged across the three NT frequency conditions separately for T and NT and for the no-prepulse and the two prepulse conditions, respectively.

Experimental design

ERP recordings and auditory discrimination performance were assessed in a placebo-controlled, double-blind, repeated measurement design. Assignment of subjects to the drug conditions (placebo, 10 and 20 mg *d*-amphetamine, respectively) was counterbalanced in order to minimize practice effects.

Test procedure

ERP recordings began 60 min after drug administration. Subjects were seated comfortably in a reclining chair in a sound-attenuated room and asked to fix a point on the wall in front of them during the recording. The procedure lasted approximately 60 min. Immediately prior to testing, subjects were presented with a practice run of 10 T and 10 NT (965 Hz) tones in a random order without prepulses. Subjects were asked to respond to the higher frequency tone by pressing a button, using the right or left hand on alternate runs. Between each block a break of approximately 3 min was allowed.

Information on the goals of the experiment was withheld from subjects until the completion of all test sessions. In particular, the delivery of prepulse stimuli was not mentioned in order to lessen the likelihood that subjects would direct their attention towards these stimuli. Subject debriefing occurred at the end of the testing sessions when subjects were asked what kind of acoustic stimuli they had heard and how they believed these were related.

ERP measurement and statistical analysis

Mean P3 amplitudes were calculated within a post-tone window of 250–500 ms for comparisons across the midline electrodes (Fz, Cz and Pz). For comparisons across prepulse, NT frequency, and drug conditions at Fz, mean P3 amplitudes were calculated using a window corresponding to maximal amplitudes at Fz (270–420 ms). PINTP was calculated at Fz as difference wave of non-target minus target ERPs in the 100-ms prepulse condition.

The P2 component of the prepulse ERP in the 500-ms prepulse condition was used as an index of attentional processing of the prepulse stimuli (cf. Michie et al. 1993). Prepulse P2 mean amplitudes were analyzed at Fz in the 500 ms prepulse condition using a post-tone window of 165–265 ms.

Mean amplitude and performance measures were analyzed with Friedman two-way ANOVAs (a non-parametric test of two or more related samples that follows a $\chi 2$ distribution). Associations between discrimination performance (reaction time, errors of commission and omission, and response bias β that is the ratio of errors of commission to errors of omission), P3 amplitude measures and amphetamine plasma levels were analyzed with Spearman rank-order correlation coefficients.

Unless otherwise stated, statistical significance was tested with $\alpha<0.05$ (two-tailed probability). By contrast, one-tailed probability was tested as a reflection of the directional nature of the following hypotheses: 1) P3b amplitude reduction is associated with decreasing decision confidence when the task is becoming difficult (Wilkinson and Seales 1978; Munte et al. 1989) and 2) *d*-amphetamine reduces frontal PINTP in association with a switch to a conservative response bias in the 100-ms prepulse condition, thus modelling similar changes observed in psychotic patients (Schall et al. 1996; Bender et al. 1999).

Drug administration and monitoring

The three test sessions were separated by approximately 1 week. The *d*-amphetamine tablets (Sigma) were dissolved in honey and administered orally. Approximately 90 min after drug administration (between recording block 3 and 4) a 15 ml blood sample was taken from the cubital vein for amphetamine plasma level assessment. Subjective drug effects were rated immediately before (baseline) and approximately 50 min after drug administration using the Addiction Research Centre Inventory (ARCI; Heartzen 1965; Heartzen and Hickey 1987). Heart rate and blood pressure were recorded before and after every session as well as every 20 min throughout the experiment. Amphetamine plasma levels were assessed using gas-chromatography (detection threshold: >2 ng/ml) with a mean re-test error rate of 7.7% (SD 6.4).

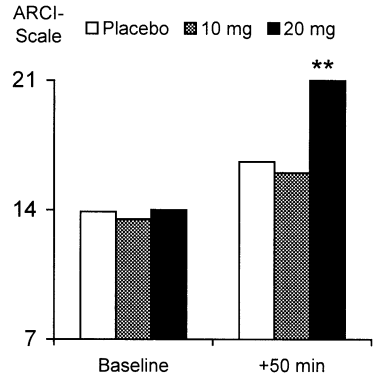


Fig. 1 Stimulant-like effects as rated on the ARCI scale immediately before and 50 min after oral administration of a placebo (*clear bars*) or 10 (*hatched bars*) or 20 mg (*black bars*) *d*-amphetamine, respectively. A significant increase of stimulant-like mood change was only confirmed for the 20 mg condition (**P<0.01)

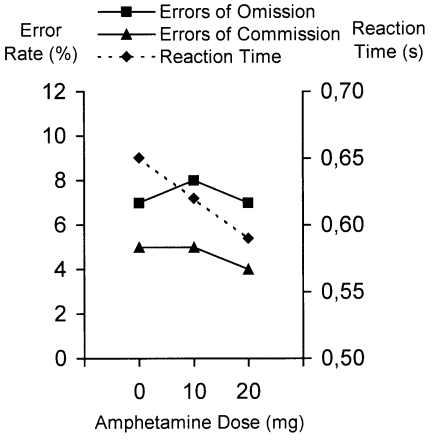


Fig. 2 Errors of omission and commission (SD 4.8–12.6%) and reaction time (SD 0.16–0.21 s) as measured in the no-prepulse condition did not differ significantly across *d*-amphetamine dose conditions. ■ Errors of omission, ▲ errors of commission, ◆ reaction time

Results

Pharmacokinetic

Mean BMI of the 12 participants was 23.9 kg/m^2 (SD 3.4). The mean amphetamine plasma level 90 min following drug administration was 15.6 ng/ml (SD 4.9) in the 10 mg and 33.4 ng/ml (SD 9.6) in the 20 mg *d*-amphetamine condition (difference: z=–3.1; P=0.002). The resulting plasma levels were significantly related to the loglinear ratio of drug intake and BMI [$F(1,22)$=17.6; P<0.001; r^2=0.83].

General pharmacodynamic effects of amphetamine

The 20 mg *d*-amphetamine dose led to a significant increase of stimulant-like effects as rated on the ARCI scale 50 min following drug-intake [Fig. 1; placebo versus high dose: $\chi 2$=6.8 (df=1), P<0.01]. No increase in ARCI-rated stimulant effects were found following 10 mg *d*-amphetamine versus placebo.

Mean reaction time (measured in the no-prepulse condition) decreased non-significantly from 0.65 s to 0.59 s (SD 0.16–0.21) with *d*-amphetamine dosage. Errors of omission and commission did not differ across drug conditions (Fig. 2).

Task difficulty effects on performance and ERP measures in the placebo condition

With increasing task difficulty, reaction time and error rates both increased significantly [35 Hz NT-T difference: 0.57 s (SD 0.18), 5.1% (SD 3.9); 25 Hz: 0.62 s (SD 0.19), 13.2% (SD 8.0); 15 Hz: 0.69 s (SD 0.21), 21.6% (SD 14.6); $\chi 2$>6.5 (df=2), P<0.05, respectively]. ERP data from two subjects were excluded from further analysis, due to EOG artefact; ERPs recorded from the remaining ten subjects included a minimum of 18 (60%) artefact free recordings in each condition [mean rejection rate: 18.3% (SD 9.8)]. Mean P3 amplitudes at Fz de-

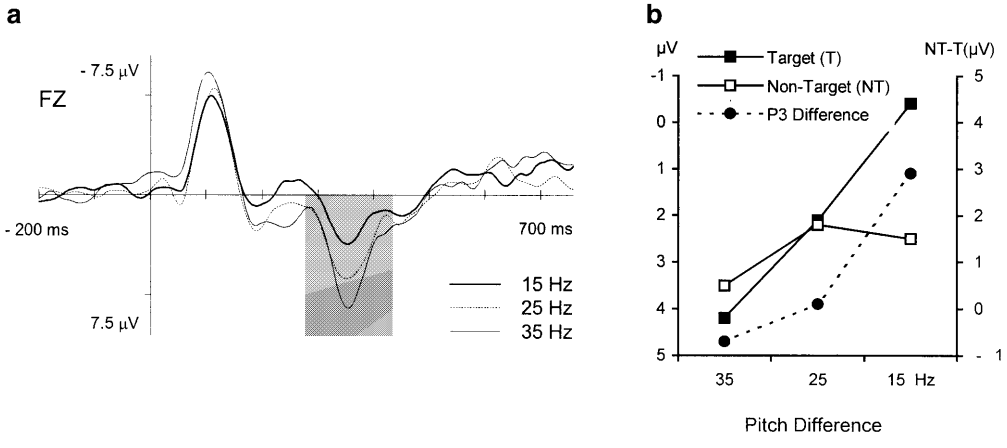


Fig. 3 a ERPs recorded in the no-prepulse placebo condition at Fz. *Dark area* indicates interval for mean amplitude measures (SD 2.6–3.4 µV). P3 amplitudes decreased with increasing difficulty of the task (P<0.04, one-tailed probability). **b** Corresponding target (T ■) and non-target (NT □) P3 mean amplitude measures. NT/T P3 differences (●) increased with increasing difficulty of the task (35–15 Hz pitch difference) due to a non-significant T-P3 reduction

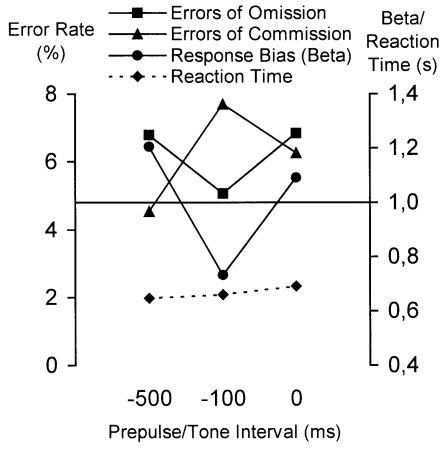


Fig. 4 Errors of omission and commission (SD 4.4–15.2%), response bias (SD 0.35–0.71) and reaction time (SD 0.2–0.24 s) in the placebo condition across prepulse conditions. The 100-ms prepulse induced a significant change from the prevailing conservative to a liberal response bias (P<0.04, one-tailed probability). ■ Errors of omission, ▲ errors of commission, ● response bias (beta), ◆ reaction time

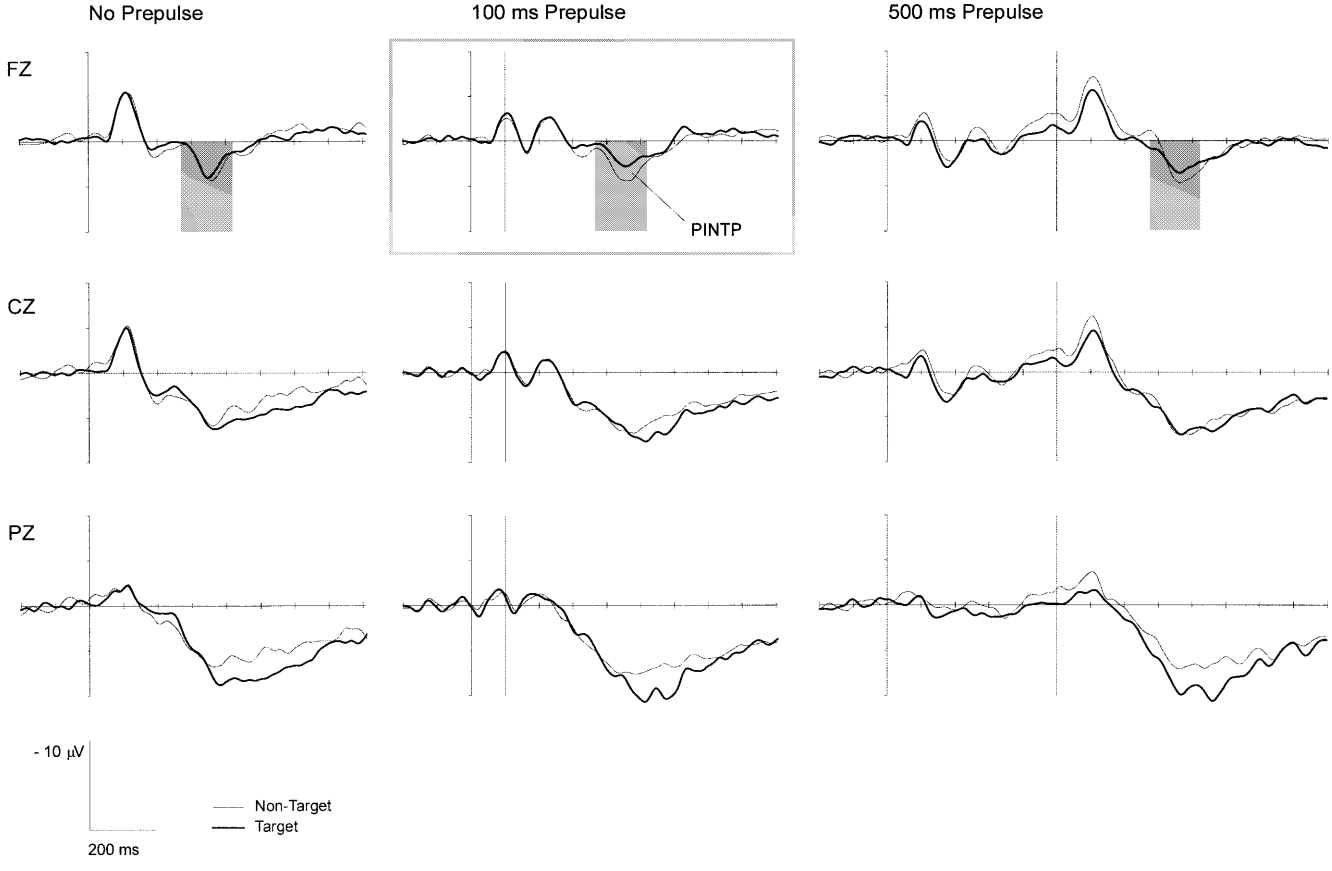
creased significantly with increasing task difficulty [35 Hz NT-T difference: 3.0 µV (SD 2.8); 25 Hz: 2.6 µV (SD 3.1); 15 Hz: 0.5 µV (SD 3.4): $\chi 2$=5.2 (df=2), P<0.04, one-tailed probability; Fig. 3a]. On the contrary, NT/T-P3 differences increased non-significantly with increasing task difficulty (Fig. 3b). There was also a non-significant association of total error rate with P3 mean amplitude measures (r_s=–0.34).

Prepulse effects on performance and P3 amplitudes in the placebo condition

Prepulse stimuli interfered with auditory discrimination performance, leading to an increasing rate of errors of commission and a decreasing rate of errors of omission in the 100-ms prepulse condition. As result, β reflected a significantly more liberal response bias [$\chi 2$=5.4 (df=2), P<0.04, one-tailed probability; Fig. 4]. Prepulse conditions had no significant effect on reaction time. PINTP was significantly larger in the 100-ms prepulse condition [across prepulse conditions at Fz: $\chi 2$=6.2 (df=2), P<0.05] at the Fz midline electrode when compared with Cz and Pz [$\chi 2$=4.7 (df=2), P<0.05, one-tailed probability; Fig. 5]. Change of PINTP and β (relative to the no-prepulse condition as baseline, respectively) significantly correlated with r_s=–0.47 (P<0.05, one-tailed probability).

Post-testing debriefing revealed that eight subjects had been aware of the prepulse. However, only two subjects reported being aware of the systematic relationship

Fig. 5 Target (*T, thick line*) and non-target (*NT, thin line*) ERPs recorded from Fz, Cz, and Pz across prepulse conditions in the placebo condition. *Dark area* indicates interval for mean amplitude measures (SD 2.8–5.2 µV). NT-P3 was significantly larger than T-P3 at Fz (P<0.05, one-tailed probability) in the 100-ms prepulse condition (P<0.05)



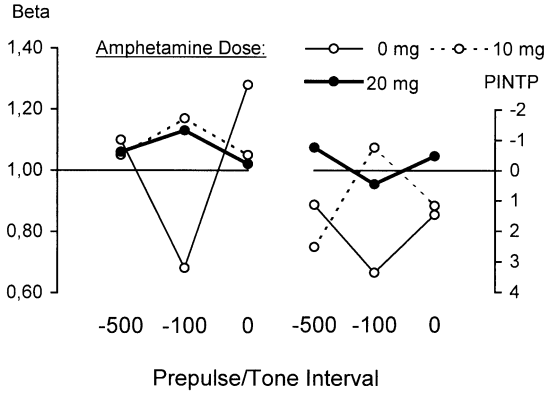


Fig. 6 Response bias (SD 0.35–0.61) and target/non-target P3 differences at Fz (SD 1.8–2.7 μV) across drug and prepulse conditions; *d*-amphetamine reversed significantly the prepulse-induced change of response bias (P<0.05, one-tailed probability). –○– 0 mg, —○— 10 mg, –●– 20 mg

between tones and prepulse clicks, while the other participants attributed the clicks to artefacts of the stimulus delivery system.

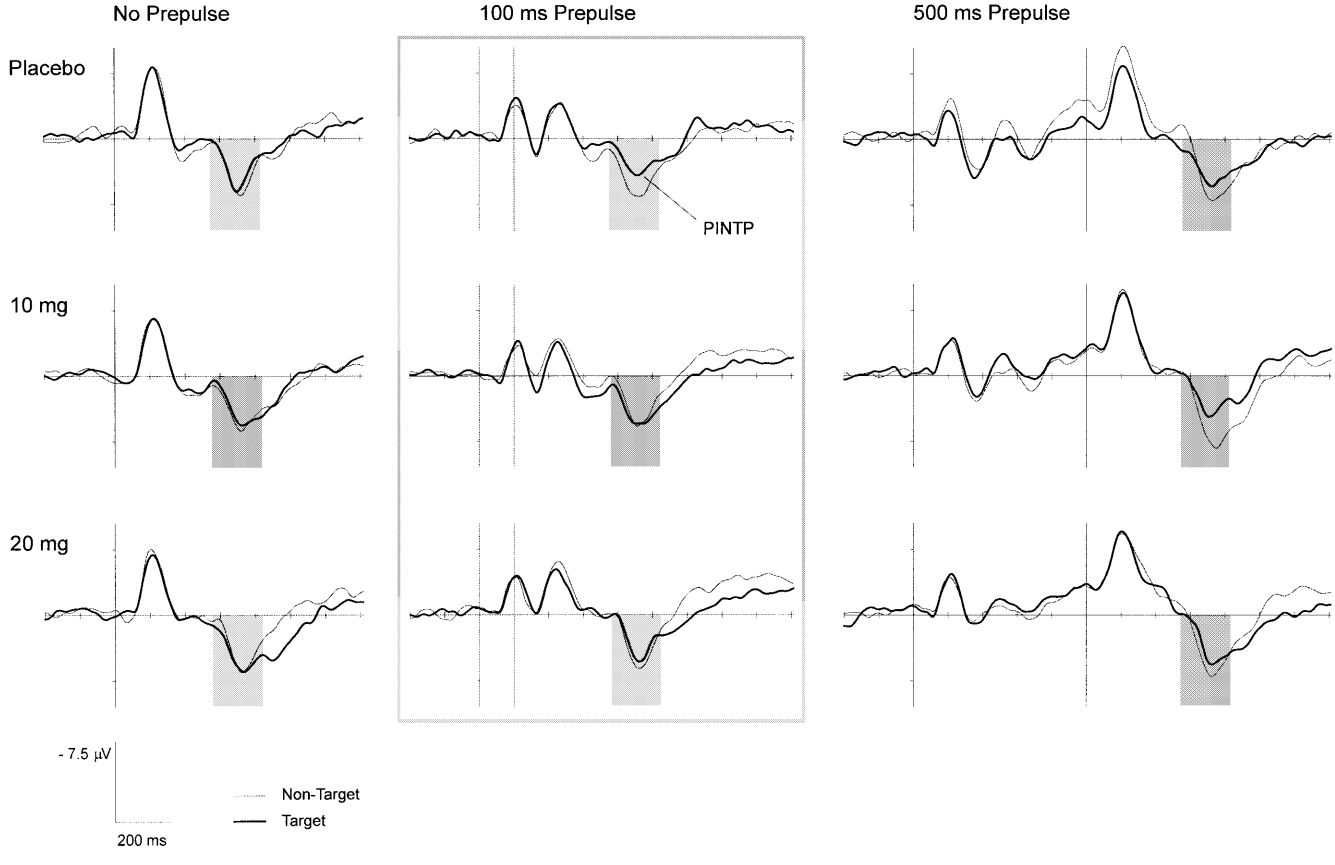
Amphetamine effect on prepulse-induced performance change and ERP measures

Amphetamine led to a significantly more conservative response bias in the 100-ms prepulse condition [10 mg: β=1.17 (SD 0.61); 20 mg: β=1.13 (SD 0.44)] compared with the placebo condition [β=0.68 (SD 0.35); $\chi 2$=4.7 (*df*=2), P<0.05, one-tailed probability; Fig. 6]. This change was associated with significantly smaller PINTP [placebo: 3.4 μV (SD 2.5), 10 mg: –0.7 μV (SD 2.7), 20 mg: 0.5 μV (SD 1.8); $\chi 2$=6.2 (*df*=2), P<0.05; Fig. 7]. PINTP reduction correlated significantly with amphetamine plasma levels across both 10 and 20 mg dose conditions (r_s=–0.53; P<0.05). Prepulse-induced changes of β and PINTP in the low and high *d*-amphetamine versus placebo condition correlated with r_s=0.58 (P<0.05; Fig. 8). Prepulse P2 positivity also decreased in a dose-dependent manner, thus suggesting greater attentional processing of the prepulse clicks in the amphetamine conditions [$\chi 2$=8.7 (*df*=2), P=0.01; Fig. 9].

Discussion

The results of the present study demonstrate that amphetamine interferes with sensory gating in an auditory discrimination task. Prepulse clicks delivered 100 ms prior to the tone stimuli altered a relatively conservative re-

Fig. 7 Target (*T, thick line*) and non-target (*NT, thin line*) ERPs recorded from Fz across prepulse and drug conditions. *Dark area* indicates interval for mean amplitude measures (SD 2.1–2.8). NT-positivity was significantly reduced under *d*-amphetamine only in the 100-ms prepulse condition (P<0.05)



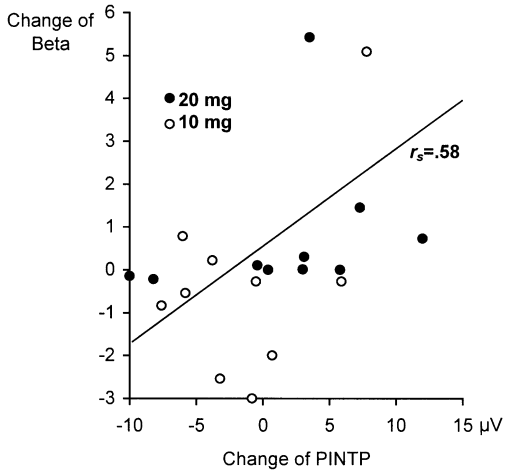


Fig. 8 Amphetamine-induced change of PINTP significantly predicted associated change of response bias (P<0.05). ● 20 mg, ○ 10 mg

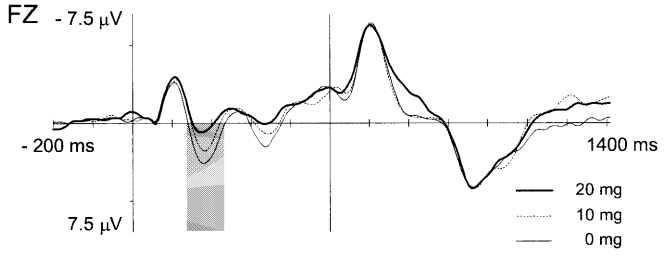


Fig. 9 Collapsed target and non-target ERPs recorded from Fz in the 500-ms prepulse condition. *Dark area* indicates interval for mean amplitude measures (SD 0.8–1.6 µV). P2-positivity of the prepulse ERP was significantly reduced in a dose-dependent manner (P=0.01) indicating an involuntary prepulse processing with increasing *d*-amphetamine dosage. — 20 mg, ... 10 mg, — 0 mg

sponse bias during the placebo condition to a more liberal response bias. This change is reversed by amphetamine and associated with PINTP reduction despite any alterations in general performance. A significant dose-effect relationship was found for P2 elicited by the prepulse click stimuli.

PINTP reduction was associated with amphetamine plasma levels and performance change. The latter relationship was already apparent in the low dose condition, in line with evidence obtained in animal studies in which sensorimotor gating was disrupted by a "threshold dose" of apomorphine of less than 0.1 mg/kg (Swerdlow et al. 1994). These data suggest that such gating is sensitive to moderate degree of dopaminergic modulation, and the absence of greater effects in the high dose condition may reflect a ceiling effect. In contrast, subjective ratings of stimulant-like effects were only significant in the high dose condition. This suggests more widespread effects, including cognitive functions other than sensory gating is required for subjective perception of stimulant-like effects of amphetamine administration. Otherwise, higher-order effects due to the order of drug administration (and not analysed here due to the small number of subjects) may have concealed a clearer result.

The present study confirmed previous reports of an increased prepulse effect on discrimination performance with increasing task difficulty (see Schall and Ward 1996). On the other hand, increased task difficulty was associated with reduced P3 amplitudes, potentially masking amphetamine effects on PINTP in the more difficult discrimination conditions. In addition, the relationship of task difficulty with reaction time and errors is also confounded by time-on-task. However, since attentional processes are probably the key mechanisms altered by the prepulse, increasing the difficulty while performing the task helps to maintain a high demand on attention which otherwise would have been reduced by learning effects.

Considering the startle reflex as an automatic, involuntary, brain stem mediated myogenic response to unexpected sudden stimuli, attention per se is not required to elicit the reflex. On the contrary, the startling event initiates an orienting reaction thus directing attention towards the stimulus or source of stimulation for evaluation (Davis 1984). It is assumed that if a startle stimulus (S2) is preceded by a non-startling stimulus (S1), S1 processing is protected from disruption caused by the competing S2 processing. This mechanism is termed "sensorimotor gating"; that is, S2 processing is inhibited by the preceding S1 processing (Hoffman and Ison 1980). Selectively directing attention towards S1 increases PPI of the startle response but not in psychotic subjects (Dawson et al. 1993). These findings indicate that attentional mechanisms are mediating sensorimotor gating and that this mediation is impaired in schizophrenia.

In the context of a S2 discrimination task as investigated here, attention is directed towards S2. Under this condition, S1 information processing has to be suppressed. As a result, S2 processing is "accentuated" in the presence of a closely preceding S1, thus leading to a lower rate of errors of omission but also to a higher false alarm rate (Schall and Ward 1996). In this respect, selectively attending S2 is reversing the inhibition process as indicated by a more liberal S2 response bias. Correspondingly, frontal NT-P3 positivity is relatively enhanced compared to the T-P3 positivity and resemble a "target-like" NT stimulus processing. Most P3 studies on selective attention are based on the oddball paradigm ("novelty reaction"=P3a and "target detection"=P3b). In contrast, PINTP is the difference wave of non-target minus target P3s recorded in a Go/NoGo procedure. Thus, PINTP is not directly related to (oddball) P3a or P3b measures although corresponding neural networks are very likely to be involved (see Introduction). However, the nature of this relationship requires further research.

Schizophrenic patients show a failure of the postulated S1 protection mechanism. Their PPI of the startle eyeblink was found to be significantly reduced (Braff et al. 1978) and correlated with neuropsychological measures of distractibility (Karper et al. 1996). The latter finding

supports the notion that schizophrenic symptoms are partly the expression of an insufficient "sensory filter" which is leading to cognitive flooding and fragmentation (Braff and Geyer 1990). As shown in the present study, *d*-amphetamine alters performance and PINTP in healthy subjects in a similar fashion to those found in patients with schizophrenia and OCD (Schall et al. 1996).

A closer look to the amphetamine-induced change of S1 processing reveals the probable underlying mode of action. Decreasing P2 positivity of the prepulse-ERP may indicate an attentional shift towards the prepulse with increasing *d*-amphetamine dosage (Michie et al. 1993; Oades et al. 1996a). This association of a smaller P2 with an attentional shift reflects the assumption that positive ERP components represent rather inhibitory than excitatory neuronal processes. "Negativity" is often related to excitation and attentional activation (i.e. processing negativity, contingent negative variation etc.). Positive ERP components are influenced by the postulated attentional excitation thus resulting in smaller amplitudes. Therefore it is concluded here that smaller P2 amplitudes indicate involuntary S1 processing which is dose-dependently promoted by dopamine-release. However, further studies investigating attentional modulation of P2 amplitudes in an auditory paired stimulus design are required to improve our understanding of the underlying mechanism.

Due to the short inter-stimulus interval of 100 ms, the capacity of a sufficient processing of the relevant S2 stimulus is reduced, particularly when the task, as used here, is difficult and the processing requires considerable resources. If the discrimination task is easy (0.8 Hz versus 1.4 kHz), healthy subjects tend to respond with a marginally increased conservative response bias in the 100-ms prepulse condition (Schall et al. 1996). However, this is probably an indication that a non-demanding task does not urge protection of processing resources from prepulse interference although this interference occurs. Within the model of sensorimotor gating, the change towards a conservative response bias in the 100-ms prepulse condition under *d*-amphetamine similar to that found in schizophrenic patients is the consequence of a "loss of protection" of S2 processing due to involuntary S1 processing.

Oades (1985) developed a model in which mesolimbic dopamine activity is postulated to be the key mediator of stimulus/response selection. He concluded that enhanced dopaminergic activity increases the probability of other competing stimuli gaining influence on the outcome of the information process. In the context of the paradigm investigated here, this "stimulus competition" appears as an involuntary attentional shift towards the non-relevant prepulse processing with increasing dopamine release. Thus high mesolimbic dopaminergic activity would lead to a breakdown of efficient stimulus control due to an sensory overflow. Considering this state as the failure of "sensory filtering", high mesolimbic dopaminergic activity could be the neural substrate for acute psychotic symptoms. In support for this assumption, a higher dopamine utilization was found particularly in psychotic patients with paranoid symptoms (Oades et al. 1994, 1996b; Oades 1997). There are also indications that neuroleptic treatment decreases "distractibility" in schizophrenic patients as measured on the digit-span test (Strauss et al. 1985). Further support for a dopaminergic modulation of selective attention derived from studies on "learned inattention". "Latent inhibition" in rats, for instance, is reduced under amphetamine, while haloperidol shows the opposite effect (Weiner 1990).

However, PPI is not modulated by dopamine release alone. A variety of neurotransmitters such as glutamate (i.e. Wan et al. 1995), serotonin (Sipes and Geyer 1995), and GABA (Kodsi and Swerdlow 1995) were found to interfere with sensorimotor gating. Accepting this complexity of interactions as a reflection of multiple input from different brain systems (e.g. crossmodal PPI; Kehne et al. 1996; Padich et al. 1996) into the resource management of information processing, it is not surprising that diminished sensorimotor gating is a common feature amongst different mental disorders like schizophrenia, Morbus Huntington (Swerdlow et al. 1995b), OCD (Swerdlow et al. 1993; Schall et al. 1996) and Gilles-de-la-Tourette syndrome (Castellanos et al. 1996).

In conclusion, by integrating PPI into an auditory S2 discrimination task, it is possible to study the neurochemical basis of selective attention behaviourally and electrophysiologically as a function of sensory gating. The results presented here suggest an involuntary attentional shift towards irrelevant information processing with increasing dopamine-release and resemble observations made in patients with schizophrenia (and OCD; Schall et al. 1996), particularly in the acute state (Bender et al. 1999). It is concluded that this procedure may provide insights into the neural mechanisms that lead to symptoms resulting from poor stimulus control and how this can be treated in a more efficient manner.

Acknowledgements The authors would like to thank Rebecca McKetin for her expert advice regarding the assessment of stimulant-like mood effects, Mark Pearson for technical assistance and the School of Pathology of the University of New South Wales for technical support. S. K. was supported by a grant of the G. A.-Lienert-Stiftung and the Sonderforschungsbereich "Neurovision" (SFB 509) of the Deutsche Forschungsgemeinschaft. U. S. was supported by a grant of the Deutsche Forschungsgemeinschaft (Scha 628/3-1).

References

Baudena P, Halgren E, Heit G, Clarke JM (1995) Intracerebral potentials to rare target and distractor auditory and visual stimuli. III. Frontal cortex. Electroencephalogr Clin Neurophysiol 94:251–264

Bender S, Schall U, Wolstein J, Grzella I, Zerbin D, Oades RD (1999) A topographic event-related potential (ERP) follow-up study on "prepulse inhibition" in first and second episode patients with schizophrenia. Psychiatry Res Neuroimaging (in press)

Braff DL, Geyer MA (1990) Sensorimotor gating and schizophrenia: human and animal model studies. Arch Gen Psychiatry 47:181–188

Braff DL, Stone C, Callaway E, Geyer M, Glick I, Bali L (1978) Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology 15:339–343

Braff DL, Grillon C, Geyer MA (1992) Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiatry 49:206–215

Campbell KB, Courchesne E, Picton TW, Squires KC (1979) Evoked potential correlates of human information processing. Biol Psychol 8:45–68

Castellanos FX, Fine EJ, Kaysen D, Marsh WL, Rapoport JL, Hallet M (1996) Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. Biol Psychiatry 39:33–41

Davis M (1984) The mammalian startle response. In: Eaten RC (ed) Neural mechanisms of startle behavior. Plenum Press, New York

Dawson ME, Hazlett EA, Filion DL, Nuechterlein KH, Schell AM (1993) Attention and schizophrenia: impaired modulation of the startle reflex. J Abnorm Psychol 102:633–641

Drewe EA (1975) Go-no go learning after frontal lobe lesions in humans. Cortex 11:8–16

Ford JM, Roth WT, Kopell BS (1976) Attention effects on auditory evoked potentials to infrequent events. Biol Psychol 4:65–77

Ford JM, Sullivan EV, Marsh L, White PM, Lim KO, Pfefferbaum A (1994) The relationship between P300 amplitude and regional gray matter volumes depends upon the attentional system engaged. Electroencephalogr Clin Neurophysiol 90:214–228

Johnson R (1993) On the neural generators of the P300 component of the event-related potential. Psychophysiology 30:90–97

Halgren E, Baudena P, Clarke JM, Heit G, Marinkovic K, Deváux B, Vignal J-P, Biraben A (1995) Intracerebral potentials to rare target and distractor auditory and visual stimuli. II. Medial, lateral and posterior temporal lobe. Electroencephalogr Clin Neurophysiol 94:229–250

Haertzen CA (1965) Addiction research center inventory (ARCI): development of a general drug estimation scale. J Nerv Ment Dis 141:300–307

Heartzen CA, Hickey JE (1987) Addiction research center inventory (ARCI): measurement of euphoria and other drug effects. In: Bozarth MA (ed) Methods of assessing the reinforcement properties of abused drugs. Springer, New York, pp 489–524

Hillyard SA, Courchesne E, Krausz HI, Picton TW (1976) Scalp topography of the P3 wave in different auditory decision tasks. In: McCallum WC, Knott JR (eds) The responsive brain. Wright, Bristol, pp 81–87

Hoffman HS, Ison JR (1980) Reflex modification in the domain of startle: I. Some empirical findings and their implications for how the nervous system processes sensory input. Psychol Rev 87:172–189

Karper LP, Freeman GK, Grillon C, Morgan C, Charney DS, Krystal JH (1996) Preliminary evidence of an association between sensorimotor gating and distractibility in psychosis. J Neuropsychiatr Clin Neurosci 8:60–66

Kehne JH, Padich RA, McCloskey TC, Taylor VL, Schmidt CJ (1996) 5-HT modulation of auditory and visual sensorimotor gating: I. Effects of 5-HT releasers on sound and light prepulse inhibition in Wistar rats. Psychopharmacology 124:95–106

Kiss I, Dashieff RM, Lordeon P (1989) A parieto-occipital generator for P300: evidence from human intracranial recordings. Int J Neuroscience 49:133–139

Knight RT (1984) Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalogr Clin Neurophysiol 59:9–20

Knight RT, Scabini D, Woods DL, Clayworth CC (1989) Contributions of temporal-parietal junction of the human auditory P3. Brain Res 502:109–116

Kodsi MH, Swerdlow NR (1995) Prepulse inhibition in the rat is regulated by ventral and caudodorsal striato-pallidal circuitry. Behav Neurosci 109:912–928

Mansbach RS, Geyer MA, Braff DL (1988) Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacology 94:507–514

McCarthy G, Wood CC (1987) Intracranial recordings of endogenous ERPs in humans. In: Ellingson RJ, Murray NMF, Halliday AM (eds) The London Symposia (EEG Suppl 39). Elsevier, Amsterdam, pp 331–337

Michie PT, Solowij N, Crawford JM, Glue LC (1993) The effects of between-source discriminability on attended and non-attended auditory ERPs. Psychophysiology 30:205–220

Milner B, Petrides M (1984) Behavioural effects of frontal lobe lesions in man. Trends Neurosci 7:403–407

Munte TF, Munte E, Heinze HJ, Scholz M (1989) Event related brain potentials and signal detection: decision confidence and signal probability. EEG EMG Z. Elektroenzephalogr Elektromygr Verwandte Geb 20:1–9

Nasman VT, Dorio PJ (1993) Reduced P3b category response in prefrontal patients. Int J Psychophysiol 14:61–74

Oades RD (1985) The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Neurosci Biobehav Rev 9:261–282

Oades RD (1997) Stimulus dimension shifts in patients with schizophrenia, with and without paranoid-hallucinatory symptoms, or obsessive compulsive disorder: strategies, blocking and monoamine status. Behav Brain Res (in press)

Oades RD, Röpke B, Eggers C (1994) Monoamine activity reflected in urine of young patients with obsessive-compulsive disorder, psychosis with and without reality distortion and healthy subjects: an exploratory analysis. J Neural Transm 96:143–159

Oades RD, Dittmann-Balcar A, Schepker R, Eggers C, Zerbin D (1996a) Auditory event-related potentials (ERPs) and mismatch negativity (MMN) in healthy children and those with attention-deficit or Tourette/tic symptoms. Biol Psychology 43:163–185

Oades RD, Zimmermann B, Eggers C (1996b) Conditioned blocking in patients with psychosis and in obsessive-compulsive disorder: association with symptoms, personality and monoamine metabolism. J Psychiatr Res 30:369–390

Padich RA, McCloskey TC, Kehne JH (1996) 5-HT modulation of auditory and visual sensorimotor gating: II. Effects of the 5-HT_{2A} antagonist MDL 100,907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats. Psychopharmacology 124:107–116

Peng RY, Mansbach RS, Braff DL, Geyer MA (1990) A D_2 dopamine receptor agonist disrupts sensorimotor gating in rats: implications for dopaminergic abnormalities in schizophremia. Neuropsychopharmacology 3:211–218

Perlstein WM, Fiorito E, Simons RF, Graham FK (1993) Lead stimulation effects on reflex blinks, exogenous brain potentials, and loudness judgements. Psychophysiology 30:347–358

Pfefferbaum A, Ford JM, Weller BJ, Kopell BS (1985) ERPs to response production and inhibition. Electroencephalogr Clin Neurophysiol 60:423–434

Putnam LE, Roth WT (1990) Effects of stimulus repetition, duration, and rise time on startle blink and automatically elicited P300. Psychophysiology 27:275–297

Ruchkin DS, Johnson R, Canoune HL, Ritter W, Hammer M (1990) Multiple sources of P3b associated with different types of information. Psychophysiology 27:157–176

Schall U, Ward PB (1996) "Prepulse inhibition" facilitates a liberal response bias in an auditory discrimination task. NeuroReport 7:652–656

Schall U, Schön A, Zerbin D, Eggers C, Oades RD (1996) Event-related potentials during an auditory discrimination with prepulse inhibition in patients with schizophrenia or obsessive-compulsive disorder and healthy subjects. Int J Neurosci 84:15–33

Schall U, Schön A, Zerbin D, Bender S, Eggers C, Oades RD (1997) A left temporal lobe impairment of auditory information processing in schizophrenia: an event-related potential study. Neurosci Lett 229:25–28

Schupp HT, Lutzenberger W, Rau H, Birbaumer N (1994) Positive shifts of event-related potentials: a state of cortical disfacilitation as reflected by the startle reflex probe. Electroencephalogr Clin Neurophysiol 90:135–144

Simson R, Vaughn HG Jr, Ritter W (1977) The scalp topography of potentials in auditory and visual discrimination tasks. Electroencephalogr Clin Neurophysiol 42:528–535

Sipes TE, Geyer MA (1995) DOI disruption of prepulse inhibition of startle in the rat is mediated by 5-HT_{2A} and not by 5-HT_{2C} receptors. Behav Pharmacol 6:839–842

Smith ME, Halgren E, Sokolik M, Baudena P, Musolino A, Liegeois-Chauvel C, Chauvel P (1990) The intracranial topography of the P3 event-related potential elicited during auditory oddball. Electroencephalogr Clin Neurophysiol 76:235–248

Spitzer RL, Williams JBW, Gibbon M, First MB (1990) Structured clinical interview for DSM-III-R. American Psychiatric Press, Washington, D.C.

Squires NK, Squires KC, Hillyard SA (1975a) Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol 38: 347–401

Squires NK, Squires KC, Hillyard SA (1975b) Decision-related cortical potentials during an auditory signal detection task with cued observation intervals. J Exp Psychol 1:268–279

Strauss ME, Lew MF, Coyle JT, Tune MD (1985) Psychopharmacologic and clinical correlates of attention in chronic schizophrenia. Am J Psychiatry 142:497–499

Sugawara M, Sadeghpour M, De Traversay J, Ornitz EM (1994) Prestimulation-induced modulation of the P300 component of event-related potentials accompanying startle in children. Electroencephalogr Clin Neurophysiol 90:201–213

Swerdlow NR, Caine SB, Geyer MA (1991) Opiate-dopamine interactions in the neural substrates of acoustic startle gating in the rat. Prog Neuropsychopharmacol Biol Psychiatry 15:415–426

Swerdlow NR, Braff DL, Taaid N, Geyer MA (1994) Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. Arch Gen Psychiatry 51:139–154

Swerdlow NR, Lipska BK, Weinberger DR, Braff DL, Jaskiw GE, Geyer MA (1995a) Increased sensitivity to the sensorimotor gating-disruptive effects of apomorphine after lesions of medial prefrontal cortex or ventral hippocampus in adult rats. Psychopharmacology 122:27–34

Swerdlow NR, Paulsen J, Braff DL, Butters N, Geyer MA, Swenson MR (1995b) Impaired prepulse inhibition of acoustic and tactile startle in patients with Huntington's disease. J Neurol Neursosurg Psychiatry 58:192–200

Verin M, Partiot A, Pillon B, Malapani C, Agid Y, Dubois B (1993) Delayed response tasks and prefrontal lesions in man – evidence for self generated patterns of behaviour with poor environmental modulation. Neuropsychologia 31:1379–1396

Verleger R, Heide W, Butt C, Kompf D (1994) Reduction of P3b in patients with temporo-parietal lesions. Brain Res Cognit Brain Res 2:103–116

Wan FJ, Geyer MA, Swerdlow NR (1995) Presynaptic dopamine-glutamate interactions in the nucleus accumbens regulate sensorimotor gating. Psychopharmacology 120:433–441

Warren JM, Akert K (1964) The frontal granular cortex and behavior. McGraw-Hill, New York, pp 313–334

Weiner I (1990) Neural substrates of latent inhibition: the switching model. Psychol Bull 108:442–461

Wilkinson RT, Seales DM (1978) EEG event-related potentials and signal detection. Biol Psychol 7:13–28