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Dose-Dependent Changes in Auditory Sensory Gating in the Prefrontal Cortex of the Cynomolgus Monkey

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Background: Sensory gating, often described as the ability to filter out irrelevant information that is repeated in close temporal proximity, is essential for the selection, processing, and storage of more salient information. This study aimed to test the effect of sensory gating under anesthesia in the prefrontal cortex (PFC) of monkeys following injection of bromocriptine, haloperidol, and phencyclidine (PCP).

Material/Methods: We used an auditory evoked potential that can be elicited by sound to examine sensory gating during treatment with haloperidol, bromocriptine, and PCP in the PFC in the cynomolgus monkey. Scalp electrodes were located in the bilateral PFC and bilateral temporal, bilateral parietal, and occipital lobes. Administration of bromocriptine (0.313 mg/kg, 0.625 mg/kg, and 1.25 mg/kg), haloperidol (0.001 mg/kg, 0.01 mg/kg, and 0.05 mg/kg), and the N-methyl-D-aspartic acid receptor antagonist PCP (0.3 mg/kg) influenced sensory gating.

Results: We demonstrated the following: (1) Administration of mid-dose bromocriptine disrupted sensory gating (N100) in the right temporal lobe, while neither low-dose nor high-dose bromocriptine impaired gating. (2) Low-dose haloperidol impaired gating in the right prefrontal cortex. Mid-dose haloperidol disrupted sensory gating in left occipital lobe. High-dose haloperidol had no obvious effect on sensory gating. (3) Gating was impaired by PCP in the left parietal lobe.

Conclusions: Our studies showed that information processing was regulated by the dopaminergic system, which might play an important role in the PFC. The dopaminergic system influenced sensory gating in a dose- and region-dependent pattern, which might modulate the different stages that receive further processing due to novel information.

MeSH Keywords: Bromocriptine • Dopamine • Haloperidol • Prefrontal Cortex • Sensory Gating

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Background

Sensory gating, which is often described as an ability to filter out irrelevant information that is repeated in close temporal proximity, is essential for the selection, processing, and storage of more salient information [1–3]. On the one hand, it protects the brain from an overload of sensory information. On the other hand, it allows the brain to make adjustments in response to changes in the environment. Both are equally important to our brain.

The prefrontal cortex (PFC) is the major projection area of dopaminergic neurons, which are located in ventral tegmental area. The subcortex of the PFC is rich in dopamine and dopaminergic neurons. Dopaminergic neurons are uniformly coupled with the pyramidal neuron synapses; the couplings may play a preferential role in determining the activities of receptors [4]. Many cognitive functions are dominated by the PFC, such as attention, working memory, and executive function [5,6]. Disorders in these functions lead to a variety of psychiatric diseases, such as schizophrenia [3,7] and attention-deficit hyperactivity disorder [8]. Sensory gating is regulated by the PFC in information processing. Studies have found that the PFC and auditory cortex are related to P50 inhibition by the auditory evoked potential (AEP) and magnetic field in healthy people [9]; focal lesions in the PFC induce a weaker suppression in patients than in healthy people [10]. By observing scalp recordings from patients with epilepsy, Korzyukov and colleagues found that the PFC and the medial temporal lobe may be substantial contributors to the process of sensory gating [11].

Dopamine, an important neurotransmitter, regulates various functions in the nervous system. Dopamine hyperactivity is one of the most important causes that leads to information processing deficit [12] and schizophrenia [13]. Many studies have shown that in the dopaminergic system in the nucleus accumbens, in which the prepulse inhibition (PPI) has been adjusted, injection of dopamine and quinpirole into the nucleus accumbens causes serious damage to the PPI [14], and administration of haloperidol can reverse this damage [15]. The effects of the dopaminergic system on sensory gating show that defects in suppression may be related to the use of the dopamine receptor agonists. For example, bromocriptine and apomorphine induce the disruption of P50 gating suppression in the healthy human [16]. In rats [17] and humans [18], sensory gating is impaired by administration of apomorphine, reducing the first sound (S1) amplitude in the cortex and hippocampus.

Disruption of gating, with its clinical symptoms of cognitive dysfunction such as sensory and attention deficit, has been considered to be a biological marker for schizophrenia [19,20]. Such symptoms are due to the diminished inhibitory capacity of the brain, which leads to an overload of irrelevant information [21] and its habituation deficits [22]. P50 suppression is not only used for the diagnosis of schizophrenia but also for relative risk assessment [23], which is also used in the diagnosis of schizotypal personality [24] and antipsychotic-free subjects at risk, as well as in first-episode and chronic patients [25].

Sensory gating can occur at different stages of information processing, such as in the AEP (the mid-latency 10 to 250 ms), and between the subconscious (P50) and conscious (N100, P200) stages. The N100 has been widely used in sensory gating research [26-28]. We examined the N100 (100 ms latency) waveform from the auditory event-related potential (ERPs) induced by the paired-click paradigm. In the paired-click paradigm, Franks et al. [29] reported directly the second sound (S2) on testing (T), the first sound on conditioning (C), and the suppression ratio (S2/S1 or T/C) in a study of manic and healthy participants. This study showed that sensory gating can be defined as the amplitude ratio (S2/S1). Low ratios represent strong suppression, and a large quantity of irrelevant information is filtered. Therefore, the purpose of the present study was to test the effect of sensory gating under anesthesia in the PFC of monkeys following injection of different drugs at several doses.

Material and Methods

Subjects

A total of 10 cynomolgus monkeys (experimental group: n=6; control group: n=4; female, mean age of 12.2±2.44 years, mean weight of 4.52±0.77 kg) from the breeding colonies at the Hainan Jingang Biological Technology Co., Ltd. were used in the experiments. The monkeys were individually housed under standard conditions (12-h light/dark cycle with light on from 07:00 to 19:00, humidity 60%, 21±2°C). The experiments were conducted in accordance with the guidelines for the National Care and Use of Animals approved by the Chinese National Animal Research Authority.

Apparatus for electroencephalogram recording

The electroencephalogram (EEG) electrodes were implanted via surgery. The cynomolgus monkeys were anesthetized with tiletamine sodium 1.25 mg/kg injected intramuscularly (i.m.) (Virbac S.A., France). The surgery was carried out under deep anesthesia, which was monitored by the toe-pinch reflex test. The monkeys were placed on a comfortable soft platform, and propofol was intravenously (i.v.) injected (1 mg/ml 0.9% NaCl), using a micro-pump at a speed of 40 ml/h. The skull was penetrated with copper wire (diameter 0.48 mm) in the bilateral frontal, temporal, parietal, occipital, left earlobe, and forehead areas, using the earlobe as the reference electrode,

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with the forehead as the ground. The remaining electrodes were used as the recording electrodes. All socket connectors (Flexible Flat Cable connector, 15 pins, Shenzhen King-hunter Technology Co., Ltd.) connected to the copper wire electrodes were inserted into an electrode pedestal. The electrodes were fixed on the scalp. Recording was performed during the day from 09:00 am to 12:00 am. The EEG signals from all electrodes were amplified and digitized by a biophysical amplifier (SynAkps 2, Neuroscan Instrument Co., Ltd., USA), which included a 32-bit A/D, band filter: 0.5–40 Hz, with an analog notch filter at 50 Hz notch, sampling rate: 1000 Hz. The data were subsequently saved and displayed on a computer. The research-grade EEG system (Neuroscan Version 4.5) used an EEG electrode fitted with eight copper wire electrodes located at F3, F4, FT7, FT8, CP3, CP4, O1, and O2. We recorded for 90 minutes every day. When experiments were completed, the recording electrodes were removed and the monkeys were gently returned to their cages.

Stimulus paradigm

The sound stimuli of the paired-click paradigm was produced by E-Prime 2.0 (Psychology Software Tools, Inc.). Two different sound stimuli (2000 Hz, 50 ms duration) were delivered with a 500 ms Inter-Stimulus Interval at 75 dB and infrequently with a 2 to 3 s random Inter-Trial Interval to prevent habituation. The sound paired-click stimuli were presented with a loudspeaker located approximately 10 cm from the monkey's head.

Data analysis

The EEG data were analyzed offline using SCAN 4.5 software [30]. The first step was manual rejection of the disturbance waveform; the data were band-filtered by a digital filter from 1 Hz, rejecting the lowest-frequency waves. The next step was extraction of the ERPs located between –100 ms and 500 ms, reduced artifacts outside of –50 mV to 50 mV. In the next step, AEP data were collected to include 100 ms prior to the stimulus and lasting for 500 ms after each stimulus was completed; the data were band-filtered by a digital filter from 40 Hz, rejecting the highest-frequency waves. At last, the waveforms of the S1 and S2 were extracted, which were computed by averaging 500 AEP trials. We defined the positive waveform that occurred at latency in 10 to 60 ms following the auditory stimuli as the P50 component, and the negative waveform that occurred within 60 to 150 ms as the N100. Peak-to-peak was calculated between the P50 and N100 peaks. The waveform amplitudes evoked by the S1 and S2 were determined as the absolute difference between the peaks of the P50 and N100 components. The ratio of S2/S1 was computed to quantify sensory gating. A value of 0 for S2/S1 indicates essentially a strong suppression, whereas a value of 1 indicates no sensory gating.

Drugs and doses

Bromocriptine (TOCRIS, UK) was dissolved in sterile saline and dosed at 0.315 mg/kg, 0.625 mg/kg, and 1.25 mg/kg. Haloperidol (Sigma, Germany) was dissolved in sterile saline and dosed at 0.001 mg/kg, 0.01 mg/kg, and 0.05 mg/kg. Phencyclidine (PCP; Chemsky [Shanghai] International Co., Ltd.) was dosed at 0.3 mg/kg. Sterile saline was administered to the control group. Drug injections were performed i.m. after 30 min. Typically, the monkeys were injected with drugs, then allowed to recover for 14 days before the next drug treatment.

Statistical analysis

All data were subsequently processed with SPSS software version 19.0 (SPSS Statistics, IBM, USA). To avoid the effect of intersubject variation, the effect of drug administration (30 to 60 min) on the S2/S1 ratio was calculated as the percent difference score from baseline (0 to 30 min). The effects of haloperidol (0.001, 0.01, 0.05 mg/kg), bromocriptine (0.313, 0.625, 1.25 mg/kg), and PCP (0.3 mg/kg) on auditory sensory gating were contrasted with the effect of saline by one-way ANOVA with repeated measure where appropriate. The effects of the cortical areas, including the right temporal lobe, the right PFC (rPFC), the left occipital lobe, and the left parietal lobe, on the amplitude, S1, and S2 were investigated using one-way ANOVA with repeated measure where appropriate. The effects of different doses of one drug were compared by one-way ANOVA with repeated measure where appropriate and the least significant difference (LSD) post hoc test. Two-way ANOVA with repeated measure where appropriate and the LSD post hoc test were used to compare haloperidol with bromocriptine. The level of significance was $P \leq 0.05$.

Results

Effects of bromocriptine administration on the PFC

Bromocriptine (0.313 mg/kg) had no obvious effect on sensory gating in the PFC or other areas compared with the control; therefore, low-dose bromocriptine did not significantly disrupt the gating in the PFC. There was a significant effect of bromocriptine (0.625 mg/kg) in the right temporal lobe relative to the control group ($P=0.03$). There was no significant difference in sensory gating in any other area. These results showed that the mid-dose bromocriptine disrupted sensory gating in the right temporal lobe, but not in the PFC. There was no significant difference in sensory gating in the presence of bromocriptine (1.25 mg/kg) compared with the control ($P>0.05$); thus, high-dose bromocriptine did not damage the PFC. With the increase in dose, increases in the ratios in CP3 (left parietal lobe), F3 (left PFC), F4 (rPFC), and FT7 (left temporal lobe)

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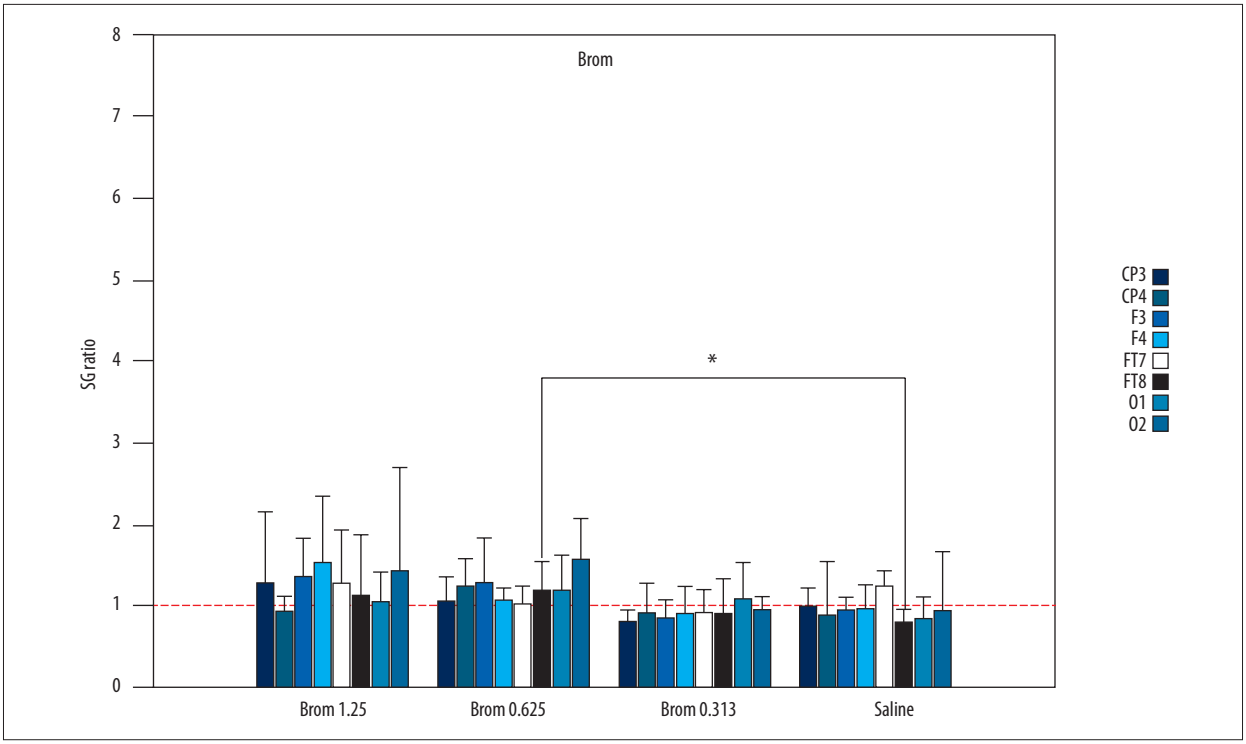

Figure 1. The effects of administration of bromocriptine on sensory gating in the PFC. Brom 0.313 – bromocriptine 0.313 mg/kg; Brom 0.625 – bromocriptine 0.625 mg/kg; Brom 1.25 – bromocriptine 1.25 mg/kg; CP3 – left parietal lobe; CP4 – right parietal lobe; F3 – left PFC; F4 – right PFC; FT7 – left temporal lobe; FT8 – right temporal lobe; O1 – left occipital area; O2 – right occipital area. The SG ratio (sensory gating ratio = SG[60–90 min]/SG[0–30] min) is shown. With Brom0.313 compared with saline, sensory gating was not significantly different in the eight areas of the brain. In the FT8, sensory gating with Brom0.625 was significantly higher than that in the saline group (P=0.03), and the remaining areas were not significantly different. Compared with the saline group, there were no significant differences in sensory gating in any of the brain areas with Brom 1.25. There was no significant difference in sensory gating between doses (P>0.05). The data are expressed as the mean ±SD. * represents P<0.05, with the one-way repeated-measures ANOVA and LSD post hoc test.

were seen. The ratio was the highest following administration of mid-dose bromocriptine in the rest of the areas, but the differences were not significant (F (1, 15)=1.444; P>0.05) (Figure 1).

Effects of administration of haloperidol in the PFC

Haloperidol (0.001 mg/kg) was compared with the control in all areas. In the rPFC, sensory gating was significantly higher following haloperidol administration compared with the control (P<0.05); in other areas, there was no significant difference. At a low dose, sensory gating was disrupted in the rPFC, but not in other areas. Sensory gating in the left occipital lobe was less suppressed following haloperidol administration (0.01 mg/kg) compared with the control (P<0.05). Mid-dose haloperidol impaired sensory gating in the left occipital lobe, but did not cause significant differences in other parts of the brain. Haloperidol (0.05 mg/kg) had no significant effect on sensory gating compared with the control in all areas. Thus, high-dose haloperidol did not impair sensory gating in the PFC. With increasing haloperidol dose, sensory gating in every brain area gradually declined. There was a significant difference between the high- and low-dose haloperidol treatments in the left parietal lobe (P<0.05), left temporal lobe (P<0.05), and rPFC (P=0.052), whereby gating was significantly lower following the high-dose treatment compared with the low dose (Figure 2).

The effects of administration of bromocriptine in contrast to haloperidol in the PFC

In contrast to haloperidol, bromocriptine had a significant effect on the sensory gating ratio in the low-dose group in the left parietal lobe (P<0.05) and the rPFC (P=0.055). Sensory gating following bromocriptine treatment was obviously lower than that following haloperidol administration. In the high-dose treatment, bromocriptine, in contrast to haloperidol, had significant effects on the rPFC (P<0.05) and the left temporal lobe (P<0.05). Sensory gating following bromocriptine was significantly higher than it was following haloperidol. The dose effects of bromocriptine and haloperidol in the PFC and other areas differed between drug treatments. Increasing the dose of bromocriptine was followed by an increase in gating, but sensory gating with the haloperidol treatments declined (Figure 3).

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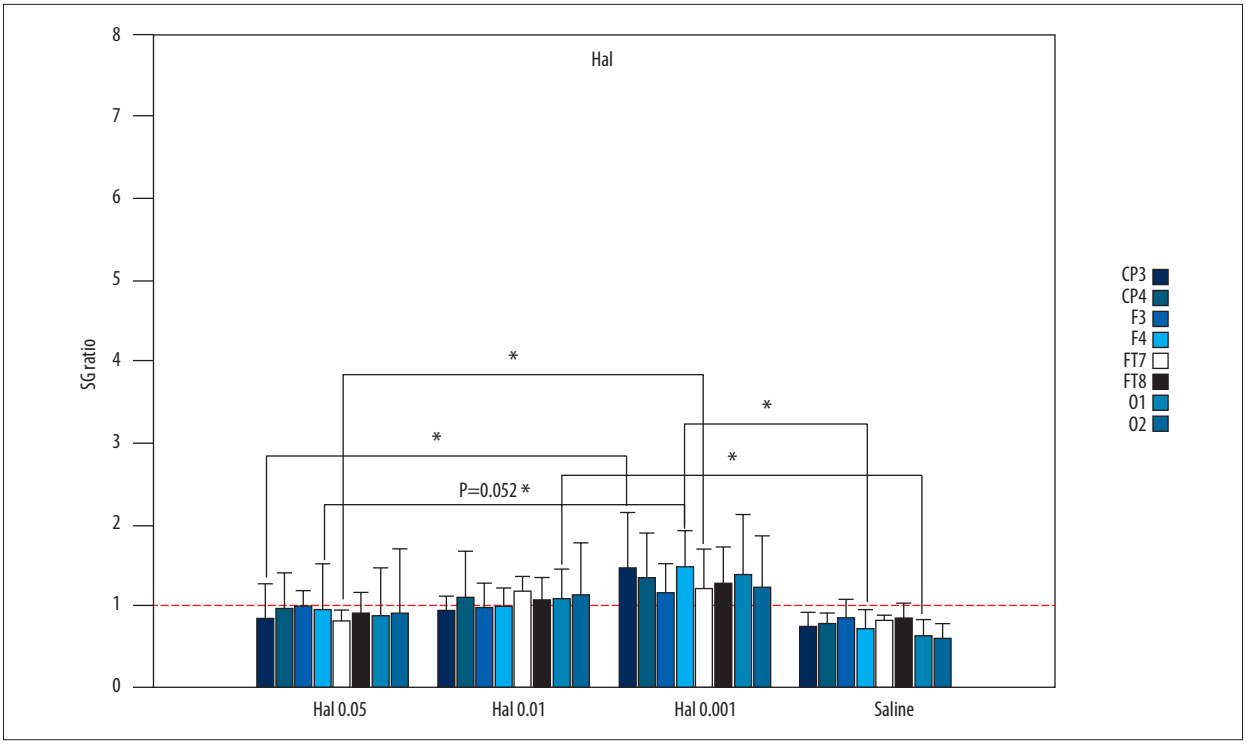

Figure 2. The effects of haloperidol administration on sensory gating in the PFC. Hal 0.001 – haloperidol 0.001 mg/kg; Hal 0.01 – haloperidol 0.01 mg/kg; Hal 0.05 – haloperidol 0.05 mg/kg. CP3 – left parietal lobe; CP4 – right parietal lobe; F3 – left PFC; F4 – right PFC; FT7 – left temporal lobe; FT8 – right temporal lobe; O1 – left occipital lobe; O2 – right occipital lobe. The SG ratio (sensory gating ratio = SG[60–90] min/SG[0–30] min) is shown. Sensory gating with Hal 0.001 was significantly higher than that in the control in the F4 (P=0.015), but no differences were observed in other areas. There was an obvious difference in the SG ratio between Hal 0.01 and control in the O1. The Hal 0.01 ratio was significantly higher than that of the control (P=0.047). There was no significant difference between the Hal 0.05 group and the control group. Hal 0.05 in CP3 (P=0.041), F4 (P=0.052), and FT7 (P=0.046) was significantly different from Hal 0.001. Sensory gating was significantly higher in the low-dose treatment than in the high-dose treatment; the remaining comparisons showed no obvious differences. The data are expressed as the mean ±SD. * represents P<0.05, with the one-way repeated-measures ANOVA and LSD post hoc test.

The effects of administration of PCP in the PFC

The effect of PCP (0.3 mg/kg) administration on sensory gating was compared with that of the control. There was no significant effect of PCP in the PFC. However, the effect of PCP (0.3 mg/kg) in the left parietal lobe was significantly higher than that of the control (P<0.05). Sensory gating in areas other than left temporal lobe also was higher than that in the control, but there was no significant difference. These results showed that PCP (0.3 mg/kg) did not cause significant suppression of sensory gating in the PFC; however, in the left parietal lobe, sensory gating was impaired (Figure 4).

Drug-dependent changes in the N100 amplitude of S1 And S2 in different cortical areas

The mid-dose of bromocriptine impaired sensory gating in the right temporal lobe. The amplitude of S1 was lower in the bromocriptine group than in the control group; however, the amplitude of S2 was not significantly different. Low-dose haloperidol disrupted sensory gating in the rPFC; this was mainly reflected in an increase in the amplitude of S2, while the increase in the amplitude of S1 was smaller. Further examination of the amplitude of S2 with mid-dose haloperidol indicated that when the differences in the amplitude of S2 and S1 in the haloperidol group relative to the control in the left occipital lobe were compared, S1 was increased to a lesser extent. PCP impaired sensory gating in the left parietal lobe, which was mainly reflected in an increase in S2; the change in S1 was not significant (Figure 5).

Discussion

In this study, we confirmed that sensory gating in the right temporal lobe was disrupted by mid-dose bromocriptine. Low-dose haloperidol damaged sensory gating in the rPFC, and mid-dose haloperidol disrupted gating in the left occipital lobe. The effect of high-dose haloperidol was less suppressive than that of other doses, as shown in the left parietal lobe, right

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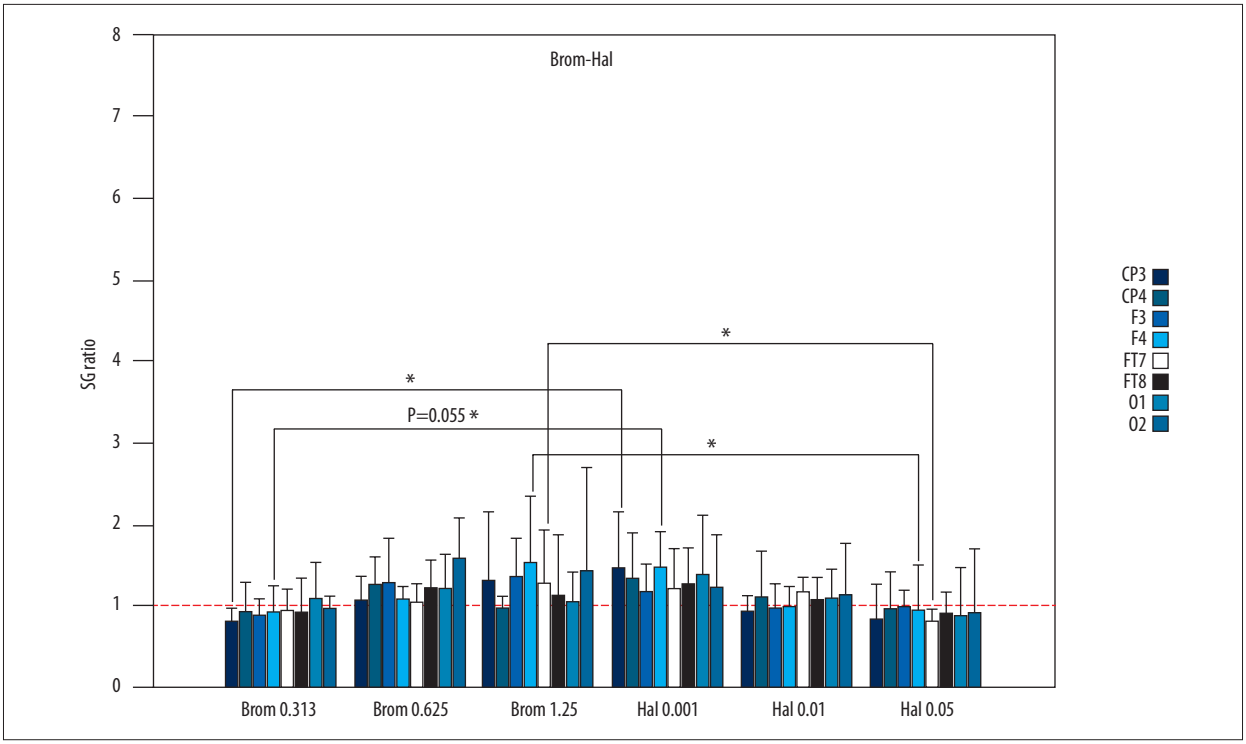

Figure 3. The effects of administration of bromocriptine compared with haloperidol in the PFC. Hal 0.001 – haloperidol 0.001 mg/kg; Hal 0.01 – haloperidol 0.01 mg/kg; Hal 0.05 – haloperidol 0.05 mg/kg. Brom 0.313, Brom 0.625, and Brom 1.25 – bromocriptine 0.313 mg/kg, bromocriptine 0.625 mg/kg, and bromocriptine 1.25 mg/kg, respectively. CP3 – left parietal lobe; CP4 – right parietal lobe; F3 – left PFC; F4 – right PFC; FT7 – left temporal lobe; FT8 – right temporal lobe; O1 – left occipital lobe; O2 – right occipital lobe. SG ratio (sensory gating ratio = SG[60–90] min/SG[0–30] min) is shown. Sensory gating in the bromocriptine group was obviously lower than that in the haloperidol group in the left parietal lobe ($P<0.05$) and the rPFC ($P=0.055$) at the low dose. At the high dose, gating in the bromocriptine group was significantly higher than that in the haloperidol group in the rPFC ($P<0.05$) and the left temporal lobe ($P<0.05$). The data are expressed as the mean ±SD. * represents $P < 0.05$, with the one-way repeated-measures ANOVA and LSD post hoc test.

prefrontal, lobe and left temporal lobe. Low-dose bromocriptine more strongly suppressed sensory gating, but high-dose haloperidol was more suppressive.

The PFC plays a leading role in the generation of P50 sensory gating. Through EEG studies [31,32], brain functional imaging of near-infrared spectroscopy [33], and functional magnetic resonance imaging [34], many studies have demonstrated that P50 gating mainly originates in the dorsolateral PFC (dlPFC), and the effects of the dlPFC in sensory gating of schizophrenia patients are more significant [34,35]. Csomor et al. showed that haloperidol can impair normally high gating [36], consistent with our observation that haloperidol (0.001 mg/kg) disrupted gating in the rPFC. This study demonstrated that disruption of gating in the PFC by haloperidol at a high dose (0.05 mg/kg) was not significant. Our results were consistent with those of Schwarzkopf et al. [37].

Many studies have reported that dysfunction of the dopaminergic system in the brain impaired sensory gating. Their experiments showed that the dopamine receptor agonists and antagonists impair gating in the healthy subject. For example, the injection of amphetamine into rats impairs N30 gating [17] and PPI [38]. The combination of bromocriptine and amphetamine reduces the inhibition of P50 in healthy subjects [39]. The increase of S1 amplitude results from the injection of haloperidol, which improves brainstem gating in rats [40]. Dopaminergic receptors were stimulated by drugs, which caused a deficit in sensory gating and PPI. This was because dopamine was overactive, and oversuppression occurred in the ventral tegmental area, ventral striatal area, nucleus accumbens, and olfactory tubercle [41]. Our studies found that mid-dose bromocriptine impaired gating in the right temporal lobe; the effects of other doses were not significant. This may have been due to the "inverted-U" dose-response of dopaminergic receptors [42]. The "inverted-U" dose-response in the PFC was confirmed in the cognitive function of animal models [43] and humans [44].

Many studies have reported that EEG changes are nonuniform in different areas; for example, the state-dependent sleep changes in auditory sensory gating in the rat are mainly reflected in the frontal and parietal regions. Changes were nonuniform in

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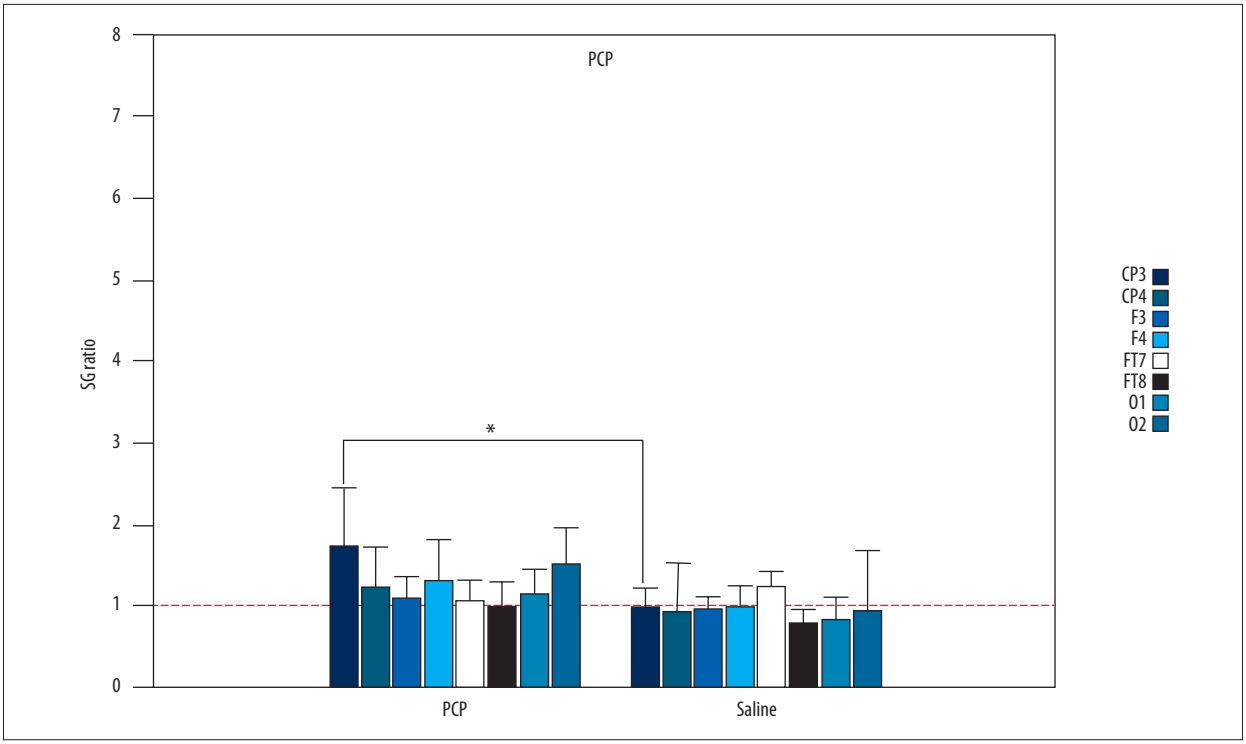

Figure 4. The effects of administration of PCP on sensory gating in the PFC. PCP – PCP (0.3 mg/kg) group; CP3 – left parietal lobe; CP4 – right parietal lobe; F3 – left PFC; F4 – right PFC; FT7 – left temporal lobe; FT8 – right temporal lobe; O1 – left occipital lobe; O2 – right occipital lobe. There was a significant difference in CP3 between the PCP and saline control groups (P=0.047), and sensory gating in the PCP group was significantly higher than that in the saline control group. Sensory gating in the PCP group was higher than that in the saline control group in the CP4, F3, F4, FT8, O1, and O2, and higher in the control group than in the PCP group in the FT7, but there was no significant difference. The data are expressed as the mean ±SD. * represents P<0.05, with the one-way repeated-measures ANOVA and LSD post hoc test.

the sensory gating of the brain regions. This may be due, firstly, to the inconsistency of signal sources on recording of the EEG; for example, the signal of the frontal cortex may be derived from frontal cortex [32], the signal of the parietal areas may originate in the hippocampus [45], and possible sources of the temporal signal are in the superior temporal gyrus [27,46]. The signal of the occipital areas was possibly derived from the auditory nerve or the middle and lower part of the brainstem [47]. This shows that the information is processed through a regional and functional dependency [48]. Secondly, the distribution of dopamine receptors in the brain was nonuniform [49].

Previous studies found that damage to sensory gating (S2/S1) was mainly reflected in two aspects. On the one hand, the amplitude of S1 was reduced and that of S2 was unchanged [28,50,51]. On the other hand, the amplitude of S2 was increased with S1 showing no changes [52,53]. The results of our experiment are consistent with those aspect. The amplitude of S1 was reduced in the bromocriptine group in the right temporal lobe. However, the amplitude of S2 was increased in the haloperidol and PCP groups in the rPFC and left parietal lobes. In animal models, the dopamine system in the brain is overactive to disrupt gating by reducing the amplitude of S1. For example, systematic injection of quinpirole into the nucleus accumbens is accompanied by a decrease in the S1 amplitude [54]. The increase in the S2 amplitude was the gating component impaired by disorders of the cholinergic system [55]. Interestingly, a subtype of dopamine D2 receptors were found in the cell body, dendrites, and axons of cholinergic interneurons in the nucleus accumbens of rats [56]. Therefore, the use of D2 receptor antagonists induces the release of acetylcholine in the striatum [57]. This also shows that injection of haloperidol and PCP may increase the function of the cholinergic system, which can induce an increase in sensory gating via a decrease in response to the S2.

Conclusions

Our study confirmed that low-dose haloperidol impaired sensory gating in the rPFC, and it was disrupted by the mid-dose in the left occipital lobe. Bromocriptine impaired sensory gating by the "inverted-U" response in a region-dependent pattern in the right temporal region, but not in the PFC. Therefore,

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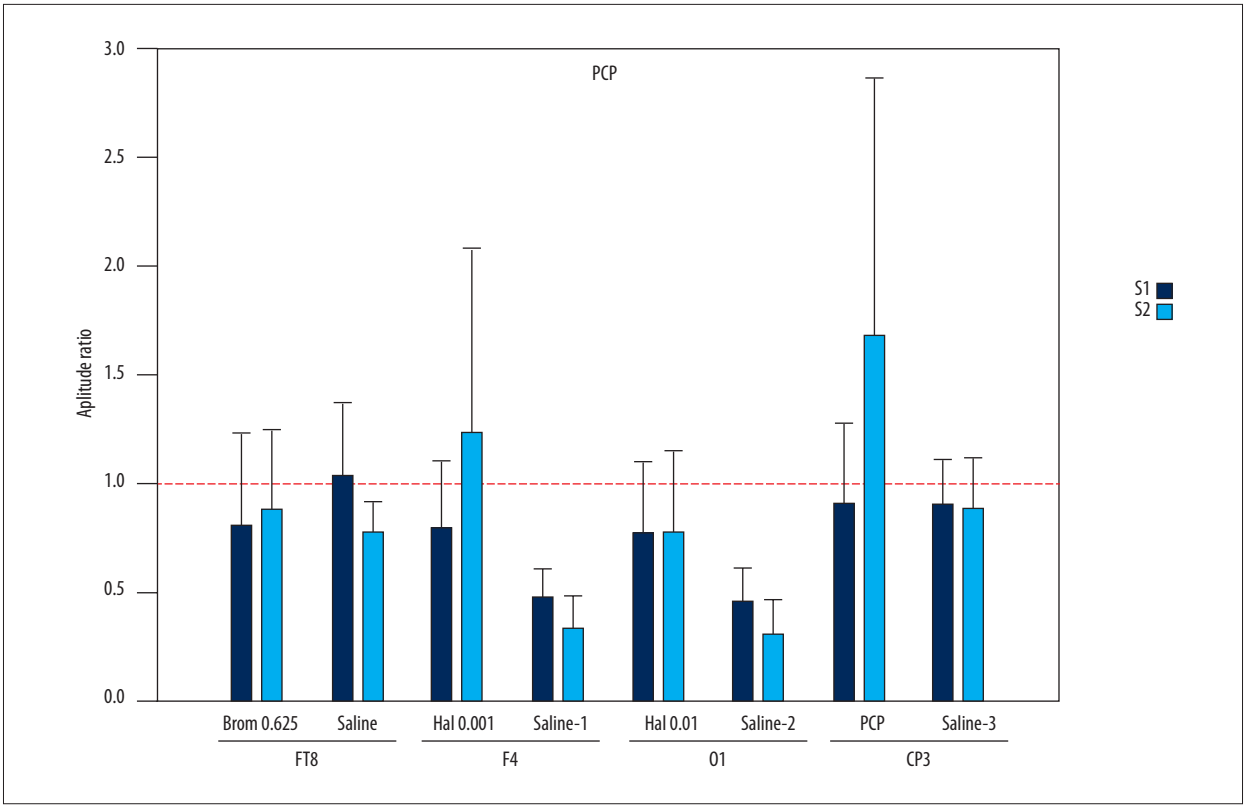

Figure 5. Drug-dependent changes in the N100 amplitude of S1 and S2 in different cortical areas. CP3, F4, FT8, and O1 represent the left parietal lobe, rPFC, right temporal lobe, and left occipital lobe, respectively. Saline, saline-1, saline-2, and saline-3 were the control group, representing the values of different areas. S1 and S2 are the first and second sounds, respectively. The amplitude ratio is the amplitude of the S1 or S2 in the 60- to 90-min interval in contrast with that of the 0- to 30-min interval. The decline in the S1 amplitude and increase in the S2 amplitude in the FT8 were compared for bromocriptine 0.625 mg/kg (Brom 0.625) and saline. Haloperidol 0.001 mg/kg (Hal 0.001) compared with saline was tested for increase of S1 and S2 amplitude in the F4. An increase in the amplitude of S1 and S2 in the O1 was recorded in the haloperidol 0.01 mg/kg (Hal 0.01) group compared with the saline group. An increase in the S2 amplitude in the CP3 was recorded in the PCP group compared with the saline group. The data are expressed as the mean ±SD. * represents $P<0.05$, with the one-way repeated-measures ANOVA and LSD post hoc tests.

our results show that the dopaminergic system plays an important role in information processing and sensory gating in the PFC, while this regulation is dose-dependent and region-dependent, which might imply that they modulate the different stages that receive further processing due to novel information.

Disclosure

This was not an industry-supported study. The authors report no conflicts of interest in this work.

References:

1. Freedman R, Adler LE, Gerhardt GA et al: Neurobiological studies of sensory gating in schizophrenia. Schizophr Bull, 1987; 13(4): 669–78
2. Freedman R, Adler LE, Myles-Worsley M et al: Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects: Hhuman recordings, computer simulation, and an animal model. Arch Gen Psychiatry, 1996; 53(12): 1114–21
3. Venables P: Input dysfunction in schizophrenia. Prog Exp Pers Res, 1963; 72: 1–47
4. Sesack SR, Deutch AY, Roth RH et al: Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. J Comp Neurol, 1989; 290(2): 213–42
5. Ghent L, Mishkin M, Teuber H-L: Short-term memory after frontal-lobe injury in man. J Comp Physiol Psychol, 1962; 55(5): 705–9
6. D'Esposito M, Postle BR: The dependence of span and delayed-response performance on prefrontal cortex. Neuropsychologia, 1999; 37(11): 1303–15
7. Adler LE, Waldo MC, Freedman R: Neurophysiologic studies of sensory gating in schizophrenia: Comparison of auditory and visual responses. Biol Psychiatry, 1985; 20(12): 1284–96.
8. Micoulaud-Franchi J-A, Lopez R, Vaillant F et al: Perceptual abnormalities related to sensory gating deficit are core symptoms in adults with ADHD. Psychiatry Res, 2015; 230(2): 357–63
9. Weisser R, Weisbrod M, Roehrig M et al: Is frontal lobe involved in the generation of auditory evoked P50? Neuroreport, 2001; 12(15): 3303–7

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10. Knight RT, Scabini D, Woods DL: Prefrontal cortex gating of auditory transmission in humans. Brain Res, 1989; 504(2): 338–42
11. Korzyukov O, Pflieger ME, Wagner M et al: Generators of the intracranial P50 response in auditory sensory gating. Neuroimage, 2007; 35(2): 814–26
12. Young AM, Ahier RG, Upton RL et al: Increased extracellular dopamine in the nucleus accumbens of the rat during associative learning of neutral stimuli. Neuroscience, 1998; 83(4): 1175–83
13. Snyder SH: The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. Am J Psychiatry, 1976; 133(2): 197–202
14. Schwarzkopf SB, Bruno JP, Mitra T: Effects of haloperidol and SCH 23390 on acoustic startle and prepulse inhibition under basal and stimulated conditions. Prog Neuropsychopharmacol Biol Psychiatry, 1993; 17(6): 1023–36
15. Wan F, Swerdlow N: Intra-accumbens infusion of quinpirole impairs sensorimotor gating of acoustic startle in rats. Psychopharmacology (Berl), 1993; 113(1): 103–9
16. Light GA, Malaspina D, Geyer MA et al: Amphetamine disrupts P50 suppression in normal subjects. Biol Psychiatry,1999; 46(7): 990–96
17. Stevens KE, Fuller LL, Rose GM: Dopaminergic and noradrenergic modulation of amphetamine-induced changes in auditory gating. Brain Res, 1991; 555(1): 91–98
18. Adler LE, Pachtman E, Franks R et al: Neurophysiological evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. Biol Psychiatry, 1982; 17(6): 639–54
19. Braff DL: Information processing and attention dysfunctions in schizophrenia. Schizophr Bull, 1993; 19(2): 233–59
20. Trystuła M, Zielińska J, Półrola P et al: Nuromarkers of anxiety in a patient with suspected schizophrenia and TIA: The effect of individuallytailored neurofeedback. Acta Neuropsychologica. 2015;13(4): 395–403
21. Freedman R, Olincy A, Ross RG et al: The genetics of sensory gating deficits in schizophrenia. Curr Psychiatry Rep, 2003; 5(2): 155–61
22. Williams LE, Blackford JU, Luksik A et al: Reduced habituation in patients with schizophrenia. Schizophr Res, 2013; 151(1): 124–32
23. Waldo MC, Cawthra E, Adler LE et al: Auditory sensory gating, hippocampal volume, and catecholamine metabolism in schizophrenics and their siblings. Schizophr Res, 1994; 12(2): 93–106
24. Cadenhead KS, Light GA, Geyer MA et al: Sensory gating deficits assessed by the P50 event-related potential in subjects with schizotypal personality disorder. Am J Psychiatry, 2000; 157(1): 55–59
25. Brockhaus-Dumke A, Schultze-Lutter F, Mueller R et al: Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients. Biol Psychiatry, 2008; 64(5): 376–84
26. Boutros NN, Belger A, Campbell D et al: Comparison of four components of sensory gating in schizophrenia and normal subjects: A preliminary report. Psychiatry Res, 1999; 88(2): 119–30
27. Boutros NN, Gjini K, Urbach H et al: Mapping repetition suppression of the N100 evoked response to the human cerebral cortex. Biol Psychiatry, 2011; 69(9): 883–89
28. Smith DM, Grant B, Fisher DJ et al: Auditory verbal hallucinations in schizophrenia correlate with P50 gating. Clin Neurophysiol, 2013; 124(7): 1329–35
29. Franks RD, Adler L, Waldo M et al: Neurophysiological studies of sensory gating in mania: Comparison with schizophrenia. Biol Psychiatry, 1983; 18(9): 989–1005
30. de Lissa P, Sorensen S, Badcock N et al: Measuring the face-sensitive N170 with a gaming EEG system: A validation study. J Neurosci Meth, 2015; 253: 47–54
31. Williams TJ, Nuechterlein KH, Subotnik KL et al: Distinct neural generators of sensory gating in schizophrenia. Psychophysiology, 2011; 48(4): 470–78
32. Liu N, Yu S, Zhou Y, et al. Age-related effects of bromocriptine on sensory gating in rhesus monkeys. NeuroReport. 2005;16(6): 603-6.
33. Ehlis AC, Ringel TM, Plichta MM et al: Cortical correlates of auditory sensory gating: A simultaneous near-infrared spectroscopy event-related potential study. Neuroscience, 2009; 159(3): 1032–43
34. Tregellas JR, Davalos DB, Rojas DC et al: Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. Schizophr Res, 2007; 92(1–3): 262–72
35. Williams TJ, Nuechterlein KH, Subotnik KL et al: Distinct neural generators of sensory gating in schizophrenia. Psychophysiology, 2011; 48(4): 470–78
36. Csomor PA, Stadler RR, Feldon J et al: Haloperidol differentially modulates prepulse inhibition and p50 suppression in healthy humans stratified for low and high gating levels. Neuropsychopharmacology, 2008; 33(3): 497–512
37. Schwarzkopf SB, Bruno JP, Mitra T: Effects of haloperidol and SCH 23390 on acoustic startle and prepulse inhibition under basal and stimulated conditions. Prog Neuropsychopharmacol Biol Psychiatry, 1993; 17(6): 1023–36
38. Swerdlow NR, Stephany N, Shoemaker JM et al: Effects of amantadine and bromocriptine on startle and sensorimotor gating: Parametric studies and cross-species comparisons. Psychopharmacology (Berl), 2002; 164(1): 82–92
39. Light GA, Malaspina D, Geyer MA et al: Amphetamine disrupts P50 suppression in normal subjects. Biol Psychiatry, 1999; 46(7): 990–96
40. Zheng J, Yang Y, Tian S et al: The dynamics of hippocampal sensory gating during the development of morphine dependence and withdrawal in rats. Neurosci Lett, 2005; 382(1): 164–68
41. Swanson LW: The projections of the ventral tegmental area and adjacent regions: A combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res Bull, 1982; 9(1–6): 321–53
42. Vijayraghavan S, Wang M, Birnbaum SG et al: Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci, 2007; 10(3): 376–84
43. Lidow MS, Koh PO, Arnsten AF: D1 dopamine receptors in the mouse prefrontal cortex: Immunocytochemical and cognitive neuropharmacological analyses. Synapse, 2003; 47(2): 101–8
44. Gibbs SE, D'Esposito M: A functional MRI study of the effects of bromocriptine, a dopamine receptor agonist, on component processes of working memory. Psychopharmacology (Berl), 2005; 180(4): 644–53
45. Vertes RP, Kocsis B: Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. Neuroscience, 1997; 81(4): 893–926
46. Tregellas JR, Davalos DB, Rojas DC et al: Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. Schizophr Res, 2007; 92(1): 262–72
47. Sekiya T, Shimamura N, Yagihashi A et al: Axonal injury in auditory nerve observed in reversible latency changes of brainstem auditory evoked potentials (BAEP) during cerebellopontine angle manipulations in rats. Hear Res, 2002; 173(1–2): 91–99
48. Schwierin B, Achermann P, Deboer T et al: Regional differences in the dynamics of the cortical EEG in the rat after sleep deprivation. Neurophysiol Clin, 1999; 110(5): 869–75
49. Seeman P: Targeting the dopamine D2 receptor in schizophrenia. Expert Opin Ther Targets, 2006; 10(4): 515–31
50. Zouridakis G, Boutros NN, Jansen BH: A fuzzy clustering approach to study the auditory P50 component in schizophrenia. Psychiatry Res, 1997; 69(2–3): 169–81
51. Patterson JV, Jin Y, Gierczak M et al: Effects of temporal variability on p50 and the gating ratio in schizophrenia: a frequency domain adaptive filter single-trial analysis. Arch Gen Psychiatry, 2000; 57(1): 57–64
52. Boutros NN, Zouridakis G, Overall J: Replication and extension of P50 findings in schizophrenia. Clin Electroencephalogr, 1991; 22(1): 40–45
53. Cullum CM, Harris JG, Waldo MC et al: Neurophysiological and neuropsychological evidence for attentional dysfunction in schizophrenia. Schizophr Res, 1993; 10(2): 131–41
54. de Bruin NM, Ellenbroek BA, van Luijtelaar EL et al: Hippocampal and cortical sensory gating in rats: Effects of quinpirole microinjections in nucleus accumbens core and shell. Neuroscience, 2001; 105(1): 169–80
55. Anstrom K, Cromwell H, Woodward D: Effects of restraint and haloperidol on sensory gating in the midbrain of awake rats. Neuroscience, 2007; 146(2): 515–24
56. Alcantara AA, Chen V, Herring BE et al: Localization of dopamine D2 receptors on cholinergic interneurons of the dorsal striatum and nucleus accumbens of the rat. Brain Res, 2003; 986(1): 22–29
57. Bertorelli R, Consolo S: D1 and D2 dopaminergic regulation of acetylcholine release from striata of freely moving rats. J Neurochem, 1990; 54(6): 2145–48

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