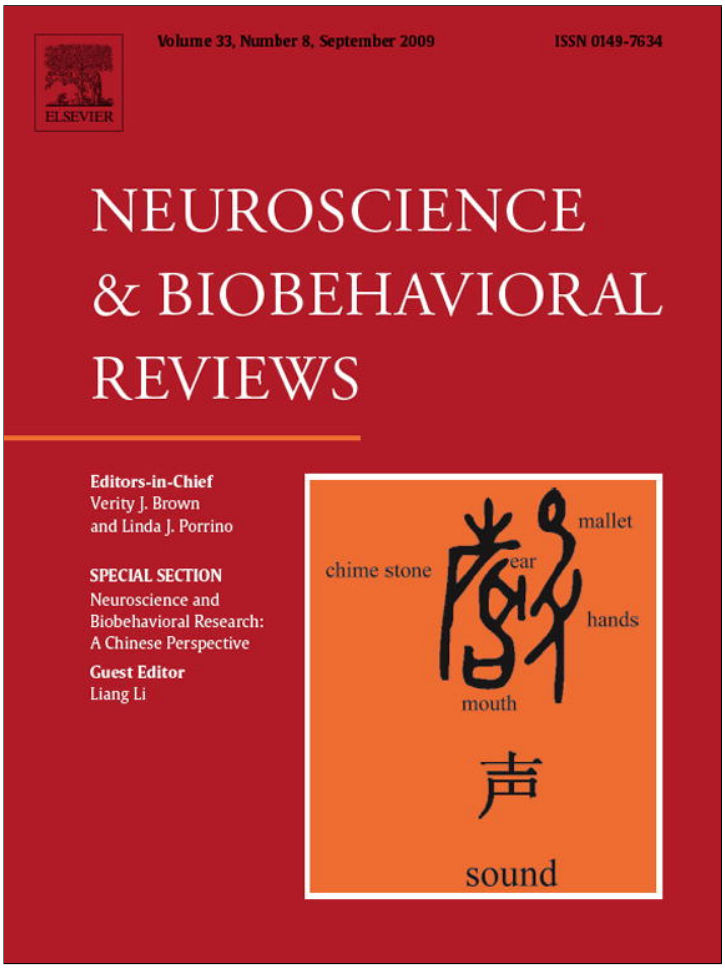

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Review

Top–down modulation of prepulse inhibition of the startle reflex in humans and rats

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ABSTRACT

Prepulse inhibition (PPI) is the attenuation of the startle reflex when the sudden intense startling stimulus is shortly preceded by a weaker, non-startling sensory stimulus (prepulse). PPI reflects a protective function of reducing disruptive influences to the processing of prepulse signals and is recognized as a model of sensorimotor gating. In humans, PPI is modulated by both attentional and emotional responses to prepulse, indicating that this early-stage gating is top–down modulated by higher-order cognitive processes. Recent studies have confirmed top–down modulation of PPI in animals, because PPI in rats is enhanced by auditory fear conditioning and perceived separation between fear-conditioned prepulse and masker. This review summarizes recent studies of top–down modulation of PPI conducted in humans and those in rats. Since both baseline PPI and attentional modulation of PPI in patients with schizophrenia are impaired, and both baseline PPI and conditional modulation of PPI in rats with isolation rearing are impaired, this review emphasizes that investigation of top–down modulation of PPI is critical for establishing new animal models for studying both cognitive features and neural bases of schizophrenia. Deficits in either baseline PPI or attentional modulation of PPI in either patients with attention-deficit/hyperactivity disorder (ADHD) or ADHD-modeling rats are also discussed.

Contents

1. The startle reflex

1.1. Circuitry, summation, and function

The startle reflex is the strongest whole-body reflexive response (Landis and Hunt, 1939), which can be easily elicited by sudden

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and intense sensory stimuli with several typical features, such as short latency, intra- and inter-modal summation, and wide dynamic ranges (e.g., Li and Frost, 1996; Li and Yeomans, 1999; Li et al., 2001).

The neural circuitry mediating startle is short. The key structure in the circuitry is the caudal pontine reticular nucleus (PnC), in which giant neurons receive axonal projections from the cochlear nucleus, trigeminal nucleus, and vestibular nucleus, and send projections to motor areas of cranial nerve nuclei (e.g., motor neurons in facial nerve nucleus) and the spinal cord (for reviews see Davis, 1984; Koch and Schnitzler, 1997; Yeomans et al., 2002). The startle reflex is the fast response to threatening stimuli and important for adaptation to the environment. The startle circuitry is able to integrate cross-modal information and facilitate the startle amplitude (Li and Yeomans, 1999; Li et al., 2001). Typically, since a head blow activates auditory, trigeminal, and vestibular systems about the same time and elicits the startle reflex with a large amplitude, the defensive pattern of the startle performance must have a critical function of protecting against head blows (Yeomans et al., 2002). However, the startle reflex also has disruptive effects on cognitive/behavioral performances. For example, the acoustic startle reflex can disrupt perception/motor tasks in humans (Foss et al., 1989a,b) and learned lever-pressing behaviors in rats (Hoffman and Overman, 1971).

1.2. Various modulation types

Accordingly, the central nervous system contains well-developed neural circuits for regulating startle responses. For example, electrical stimulation of each of the following three brain structures has different effects on the acoustic startle reflex in awake rats: the amygdala, ventral pallidum, and inferior colliculus (IC) (Li et al., 1999) (Fig. 1). The magnitude of the startle reflex can be enhanced by fear (Bradley et al., 1993, 2006; Grillon and Davis, 1997; Greenwald et al., 1998; Stanley and Knight, 2004; Vanman et al., 1996; Volz et al., 2003; Waters et al., 2005), and the amygdala plays a critical role in the fear potentiation of startle (Hitchcock and Davis, 1987). Thus electrical stimulation of the amygdala enhances the acoustic startle, mimicking fear potentiation of startle (the curve with open circles in Fig. 1). The ventral pallidum, a basal forebrain structure, occupies a position as an interface between the limbic system and the motor system and is involved in both the initiation of motor activity (e.g., Austin and Kalivas, 1991) and the induction of intracranial self-stimulation performance (e.g., Panagis et al., 1997). Mogenson et al. (1980) suggested that the ventral pallidum mediates the flow of motivationally relevant information to motor systems, and regulates the feedback of this mediation. Thus the startle inhibition caused by electrical stimulation of the ventral pallidum (the curve with filled circles in Fig. 1) reflects the motive-motor gating process. The IC is an auditory midbrain structure occupying a critical position in the auditory ascending system. It is also a relay station in the pathway mediating sensorimotor gating (for a review see Li and Yue, 2002). The startle inhibition caused by electrical stimulation of the IC (the curve with open triangles in Fig. 1) exhibits a sensorimotor gating effect.

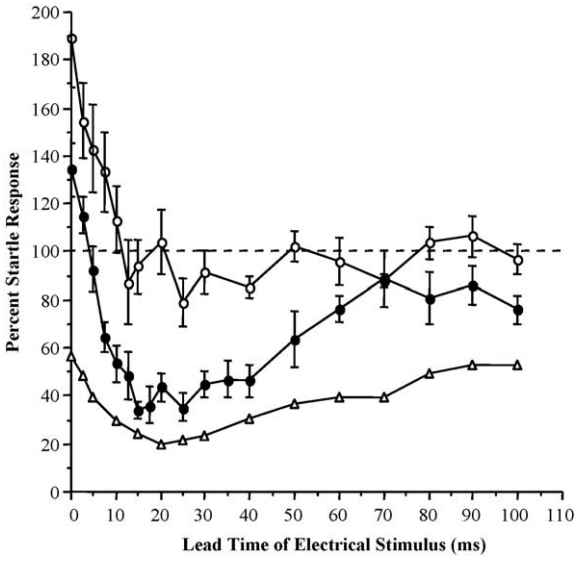

Fig. 1. Effects of electrical stimulation of one of the following brain structures on acoustic startle responses to a startling noise burst at various inter-stimulus intervals: bilateral amygdala (open circles), bilateral ventral pallidum (filled circles), and unilateral inferior colliculus (triangles). The mean normalized response to the startling noise burst alone is indicated by the broken line. This figure was adapted from Li et al. (1999).

2. Prepulse inhibition: a model of sensorimotor gating

Prepulse inhibition (PPI) is the normal reduction of the amplitude of the startle reflex in response to an intense startling stimulus (pulse) when this intense stimulus is shortly preceded by a weaker, non-startling sensory stimulus (prepulse) (Buckland et al., 1969; Hoffman and Searle, 1965; Ison and Hammond, 1971; Pickney, 1976; for a classic review see Hoffman and Ison, 1980). Graham (1975) proposed a "protection-of-processing" theory for justifying the function of PPI: a weak prepulse stimulus followed by an intense stimulus can trigger not only the information processing for the prepulse signal but also a gating mechanism that dampens the information of the intense disruptive inputs. Therefore PPI protects the early processing of the prepulse signal from interference by extraneous stimuli. Since the consequences of PPI include the reduction of behavioral responses to disruptive stimuli by regulating the motor system and/or the pre-motor system, PPI has been generally recognized as a simple operational measure of sensorimotor gating (e.g., Swerdlow et al., 1991).

The protecting or facilitating effects of PPI on central processing of the prepulse signal have been experimentally demonstrated in humans. For example, presentation of a weak acoustic stimulus 100 ms prior to a startle-eliciting stimulus significantly reduces startle-produced errors in an aiming task (Foss et al., 1989a,b), and the accuracy of discriminating the prepulse stimulus is highly correlated to the degree of suppression of the startle reflex (Norris and Blumenthal, 1996; Perlstein et al., 1993). However, to our knowledge, there is a lack of the literature on whether PPI also plays a role in protecting/facilitating the central processing of prepulse signals in laboratory animals.

3. Neural circuitry mediating PPI

PPI can be observed in laboratory rats with either acutely surgical decerebration (Davis and Gendelman, 1977; Fox, 1979; Li and Frost, 2000) or chemically suppressed cortex (Ison et al., 1991) and in humans during sleep (Silverstein et al., 1980), indicating that the basic neural circuitry for mediating PPI must reside in the brainstem and PPI primarily reflects an automatic process at the pre-attentive stage. Animal studies have shown that one of the anatomical models for explaining the circuitry mediating auditory PPI includes the serially connected three midbrain structures: the IC (Leitner and Cohen, 1985; Li et al., 1998a,b), deeper layers of the superior colliculus (DpSC) and the intermediate layers of the superior colliculus (Fendt, 1999; Fendt et al., 1994; Li and Yeomans, 2000; Yeomans et al., 2006), and the pedunculopontine tegmental nucleus (PPTg) (Koch et al., 1993; Kodsi and Swerdlow, 1997; Swerdlow and Geyer, 1993) (Fig. 2). The IC sends vast axonal projections to the DpSC from the dorsomedial region, the external

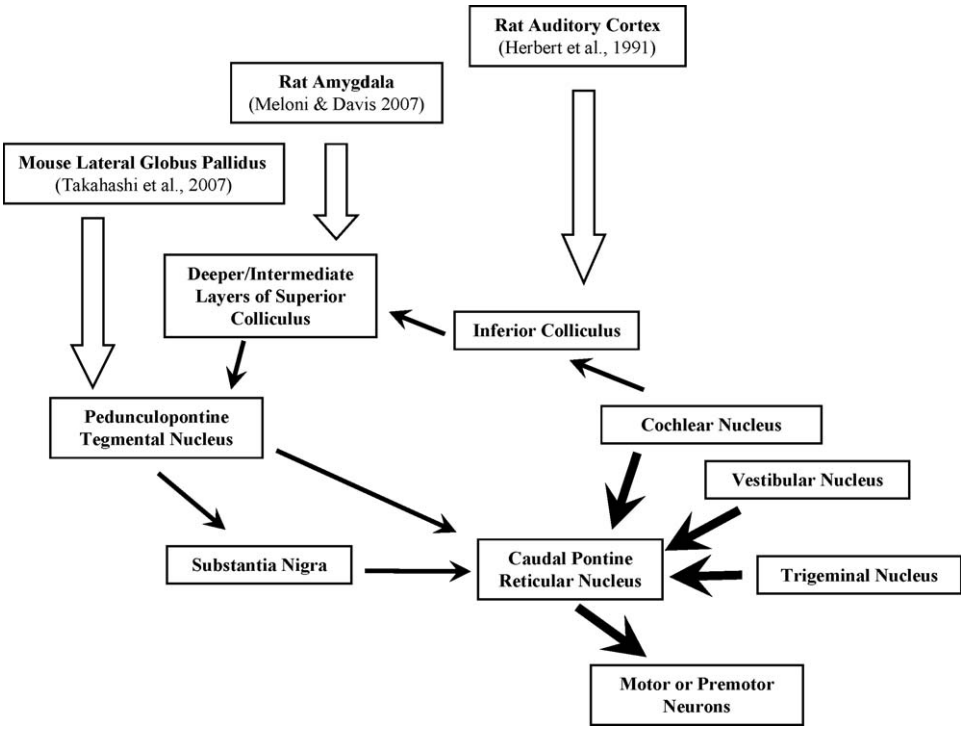

Fig. 2. Neural pathways mediating (1) startle responses (thick black arrows), (2) auditory prepulse inhibition (thin black arrows), and (3) modulation of prepulse inhibition (thick unfilled arrows). The caudal pontine reticular nucleus receives axonal projections from the cochlear nucleus, trigeminal nucleus, and vestibular nucleus, and sends projections to motor neurons in cranial nerve nuclei and the spinal cord. The inferior colliculus receives projection from the lower auditory brainstem and sends projections to the deep/intermediate layers of the superior colliculus, which in turn, project to the pedunculopontine tegmental nucleus (PPTg). The PPTg modulates neural activity in the caudal pontine reticular nucleus both by direct projections and via the relay of substantia nigra. Three forebrain structures have been reported to have direct projections to the prepulse inhibition circuitry: lateral globus pallidus, amygdala, and auditory cortex.

nucleus, and the nucleus of the brachium of the IC, the DpSC in turn project to the PPTg, and finally the PPTg affects the PnC (the obligatory relay station in the primary startle pathway for integrating prepulse and startling signals) both directly by direct projections and indirectly via the relay of substantia nigra (for reviews see Fendt et al., 2001; Li and Yue, 2002). However, recent studies have also suggested that some components in the circuitry mediating PPI bypass the DpSC (Yeomans et al., 2006) or even the PPTg and PnC (Gomez-Nieto et al., 2008). Thus there may be multiple pathways for mediating PPI.

Although the primary circuitry mediating PPI is located in the brainstem, numerous studies using human participants or rats have confirmed that PPI can be modulated by higher-order cognitive processes (e.g., attentional modulation and conditional modulation, see below). Thus the circuitry mediating PPI must receive top–down regulations via descending axonal projections from forebrain structures. In rodents, it has been reported that the IC, DpSC, and PPTg receive direct axonal projections from the auditory cortex (Herbert et al., 1991), amygdala (Meloni and Davis, 2007), and lateral globus pallidus (Takahashi et al., 2007), respectively (Fig. 2).

4. Attentional modulation of PPI in humans

In humans, PPI is usually measured as a change in the eyeblink reflex which is one of the components of the startle reflex. Sufficient evidence confirms that directing attention to the prepulse signal enhances PPI (e.g., Ashare et al., 2007; Bohmelt et al., 1999; Cornwell et al., 2008; Dawson et al., 1993, 2000; Elden and Flaten, 2002, 2003; Filion et al., 1993; Filion and Poje, 2003; Hawk et al., 2002; Hazlett et al., 1998; Heekeren et al., 2004; Hutchison et al., 2003; Jennings et al., 1996; Schell et al., 2000; Thorne et al., 2005). In the "attention-to-prepulse" paradigm (task-based protocol), the prepulse stimuli are a series of intermixed high- and low-pitch tones of short and long durations, and participants are instructed to attend to tones of one pitch and to ignore tones of the other pitch by, for example, counting silently the number of longer-duration higher (or lower) -pitch tones and simply ignoring the other pitch (Filion et al., 1993). Filion et al. demonstrated that human participants who attended the prepulse exhibited larger PPI at the prepulse lead time (inter-stimulus interval, ISI, the onset interval between the prepulse and startling stimulus) of 120 ms compared to participants who ignored the prepulse. The attentional modulation effect on PPI has been demonstrated for the prepulse lead time of 120 ms but not for that of 60 or 240 ms (e.g., Ashare et al., 2007; Bohmelt et al., 1999; Filion et al., 1993; Hawk et al., 2002; Jennings et al., 1996; Schell et al., 2000). Dawson et al. (1993) suggested that pre-attentive stimulus detection and evaluation occur at the prepulse lead time of about 60 ms, stimulus discrimination and further attentional allocation occur at the lead time of about 120 ms, and transition from stimulus evaluation to judgment occurs at the lead time of about 240 ms. However, Filion and Poje (2003) reported that even at the ISI of 60 ms PPI in task-based protocol (when the prepulse was attended or ignored) was larger than that in passive, no-task protocol. They suggested that PPI at the ISI of 60 ms in task-based protocol is a sign of sensorimotor gating enhanced by the initial nonselective allocation of attention to both attended and ignored prepulses. Moreover, Heekeren et al. (2004) reported that when participants directed their attention to both the prepulse and the startling pulse, an increased PPI occurred at the ISI of 240 ms but not the shorter ISI of 100 ms. Thus, attention to a prepulse has not only a typical time-locked modulatory influence to PPI but also complicated underlying mechanisms.

PPI in humans can also be enhanced if the prepulse stimulus becomes affective. For example, Bradley et al. (2006) have shown

that eyeblink startle responses to a white-noise burst (103 dB, 50 ms in duration) can be markedly inhibited by the presentation of a picture as the prepulse when the onset delay between the visual stimulus and the startling stimulus is 300 ms. Interestingly, the startle inhibition is affected by the content of the picture: either pleasant or unpleasant pictures cause larger inhibition than neutral pictures. Moreover, even anticipation of electrical shock can increase general vigilance, enhance processing of the prepulse stimulus, and augment PPI (Grillon and Davis, 1997). These reports suggest that affective stimuli draw more attentional resources than neutral stimuli and produce greater PPI. Clearly, the whole PPI profile is not solely an automatic process, instead, it has both low-level involuntary (automatic) and high-level-controlled components (e.g., Dawson et al., 1993; Elden and Flaten, 2002).

5. fMRI studies of brain structures modulating PPI in humans

Animal studies have suggested that PPI is modulated by the cortico-striatal-pallido-thalamic circuitry that includes the prefrontal cortex, thalamus, amygdala, hippocampus, nucleus accumbens, striatum, ventral pallidum, and globus pallidum (for a review see Swerdlow et al., 2001). Recently, functional magnetic resonance imaging (fMRI) studies in humans appear to confirm the involvement of some of these brain structures in PPI (e.g., Campbell et al., 2007; Goldman et al., 2006; Hazlett et al., 2001; Kumari et al., 2007). However, both methods and results noticeably differ across these brain-imaging studies.

In the Kumari et al. study (2007), compared to the condition of startling pulse alone, the condition with the prepulse at the lead time of 120 ms caused increased blood-oxygen-level-dependent (BOLD) in globus pallidus, putamen, caudate, thalamus, insular inferior frontal cortex, temporal cortex, inferior parietal cortex, and hippocampus. In the Goldman et al. study (2006), compared to the condition with startling pulse alone, the amplitude of the hemodynamic response function for the condition with the prepulse (lead time = 120 ms) was found to be increased in the auditory cortices and anterior insula, while decreased in the cerebellum, thalamus and anterior cingulate cortex. It should be noted that the comparison of the BOLD between the "prepulse + pulse" condition causing PPI with the "startling pulse alone" condition may reflect the neural activation that is associated with either the central representation of the prepulse or a difference in stimulus energy.

The comparison of the BOLD between the "prepulse + pulse" condition causing PPI with the "prepulse + pulse" condition not causing PPI appears to be more appropriate for revealing the biological correlates of PPI (Campbell et al., 2007). Campbell et al. reported that compared to the condition of the prepulse lead time of 480 ms (which did not cause significant startle inhibition), with the condition of the prepulse lead time of 120 ms led to a BOLD increase in the left middle frontal, right superior frontal and right precentral gyri. Hazlett et al. (2001) introduced an attention-to-prepulse paradigm in their fMRI study and reported that in the anterior and mediodorsal nuclei of the thalamus, the BOLD activation was greater under the "attended tone + startle noise" condition than that under the "ignored tone + startle noise" condition, suggesting a thalamic involvement in attentional modulation of PPI.

When both the prepulse and startling pulse are presented with a short interval, it is still not clear whether the fMRI method is sufficiently reliable to separate the hemodynamic representation of sensory gating (elicited by the prepulse and/or the startling pulse) from that of sensory processing (elicited by the prepulse and/or the startling pulse), particularly when the duration of the prepulse is several seconds as used in some fMRI studies. Based on the "protection-of-processing" theory proposed by Graham (1975), comparisons of prepulse-induced changes in the central consequence of the startling pulse across conditions should be primarily investigated, because the extent of suppression of the central consequence of the startling pulse is closely correlated with the degree of prepulse-induced gating of the startling stimulus. On the other hand, the startling stimulus itself also elicits central gating activities. When the stimulus-duration effect is controlled, due to its higher sound level, the startling pulse itself must elicit sensory gating with a different extent compared to the weaker prepulse. Thus the discrimination of the prepulse-induced gating correlates from the pulse-induced gating correlates must be under serious consideration in fMRI studies.

6. Fear conditioning modulates PPI in laboratory rats

In humans, emotional prepulse stimuli can elicit larger PPI than emotionally neutral prepulse stimuli (Bradley et al., 2006). Particularly, Cornwell et al. (2008) reported that in humans when a prepulse (air puff or pure-tone burst) occurred under conditions associated with relatively predictable timing of shock delivery, PPI was significantly higher than when the prepulse was associated with either more unpredictable timing of shock delivery or safe conditions without shock delivery. Thus it is important to know whether fear conditioning of a prepulse is able to modulate PPI in laboratory rats.

Recent studies conducted in our laboratory have shown that PPI can be enhanced in normal (socially reared) rats by auditory fear conditioning (AFC), which is induced by precisely pairing the prepulse stimulus with footshock (Du et al., 2009; Huang et al., 2007; Li et al., 2008; Zou et al., 2007). One type of prepulse stimulus used for this line of studies is the silent gap embedded in otherwise continuous noise sound, which is delivered by each of the two spatially separated loudspeakers. It is well known that the temporal resolution of the auditory system is the ability to discriminate rapid changes in the envelope of a sound, and a common way of investigating temporal resolution in both humans and animals is the measurement of the threshold of detecting a gap embedded in an otherwise continuous sound. The gap-detection ability is determined in part by the rate of decay of neural activity during the gap and in part by sensitivity to the signal increment at the end of the gap (Plomp, 1964). Thus, compared to the detection of a sound burst, the detection of a gap involves more perceptual and/or cognitive components. The gap has been successfully used as a prepulse in the PPI paradigm (Barsz et al., 1998, 2002; Ison et al., 1998; Ison and Bowen, 2000; Leitner and Girten, 1997). Unlike a sound-burst prepulse whose salience depends on the sound level of the prepulse (Li et al., 1998a), a gap prepulse can inhibit the startle reflex with different extents by varying the gap size without changing the sound level of the markers (or called carriers, the sounds before and after the gap). Generally, with increasing the size of a gap embedded in noise markers from 0 to 40 ms, the inhibitory effect of the gap prepulse on the acoustic startle reflex increases monotonically in rats (Zou et al., 2007). Following temporally combining a gap with footshock in a precise manner, the gap becomes conditioned, and gap-induced PPI is significantly enhanced (Li et al., 2008; Zou et al., 2007) (Fig. 3). Thus when the gap prepulse becomes a signal informing aversive events, it elicits larger sensorimotor gating effects, compared to when it has not been conditioned.

As mentioned above, in humans the processing of the prepulse stimulus is highly correlated to the degree of PPI (Filion and Ciranni, 1994; Mussat-Whitlow and Blumenthal, 1997; Norris and Blumenthal, 1995, 1996; Perlstein et al., 1989, 1993) and attention to the prepulse can enhance PPI (Dawson et al., 2000; Filion and Ciranni, 1994; Filion et al., 1993; Filion and Poje, 2003; Jennings et al., 1996; Schell et al., 2000; Thorne et al., 2005). Thus it is suggested that fear conditioning of the prepulse stimulus drives rats to be alert in listening to room acoustics, facilitates rats' attention to the prepulse stimulus, builds up deeper central

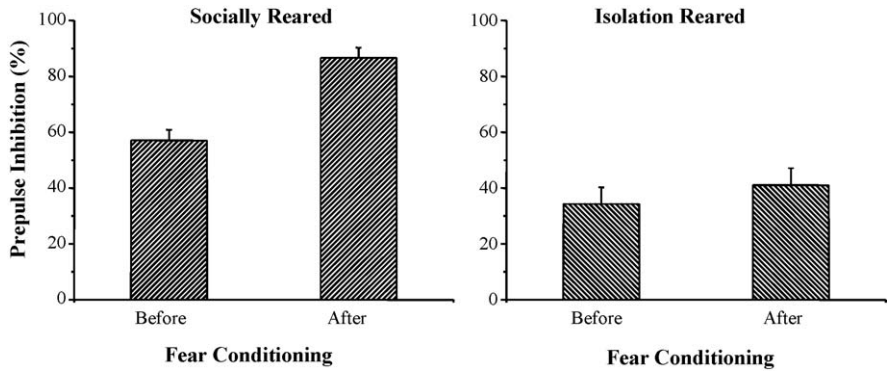

Fig. 3. Comparison of normalized group-mean magnitude of prepulse inhibition before and after auditory fear-conditioning manipulation in socially-reared rats and isolation-reared rats. Note that fear conditioning leads to a significantly enhancing effect on prepulse inhibition in socially-reared rats but a much weaker enhancing effect in isolation-reared rats. This figure was adapted from Li et al. (2008) with modification.

processing of the prepulse stimulus, and eventually leads to the enhancement of PPI.

Röskam and Koch (2006) reported that after the fear-conditioned acoustic prepulse (10 kHz tone with the duration of 300 ms and the sound pressure level of 72 dB) was further conditioned by a 300-ms light flash (the visual conditioned inhibitor) which indicated that the fear-conditioned tone would not be followed by footshock, presenting the conditioned light inhibitor 300 ms before the startling noise pulse significantly enhanced PPI in rats. However, presenting the double-conditioned acoustic prepulse (after training for conditioned inhibition) did not enhance PPI. Since the authors did not report whether PPI was enhanced just after the prepulse tone was fear conditioned, it is not clear whether auditory fear extinction (AFE) played a role in weakening the effect of AFC. The condition-inhibition paradigm established by Röskam and Koch (2006) would be useful for adjusting the degree of rats' attention to the fear-conditioned acoustic prepulse.

Baschnagel et al. (2007) reported that after the 1-s acoustic prepulse (an intensity increase in background white-noise) was precisely paired with the water presentation in water-deprived rats, PPI was typically reduced at the prepulse lead time of 60 ms. As speculated by the authors, an increase of central release of dopamine elicited by water reward might be a cause for reducing PPI. Thus the authors suggested that "biologically salient appetitive prepulse presented to rats do not have the same effect that attended prepulses have on PPI "in humans".

7. Perceived spatial separation between prepulse and masking noise enhances PPI

To further advance the model for more specifically studying attentional modulation of PPI in rats, we recently investigated whether perceived spatial separation between prepulse and noise masker enhances PPI in socially-reared rats and isolation-reared rats (Du et al., 2009).

In a noisy, reverberant environment, listeners receive not only sound waves that directly emanate from various sources but also reflections from surfaces at various locations. In such an environment, to perceptually segregate a target signal from other disruptive stimuli (which will not be as highly correlated with the target signal), the auditory system must not only integrate sound waves that directly come from the signal source with reflections of the signal source, but also at the same time, integrate sound waves that come from a disruptive source with reflections of the disruptive source. Otherwise the auditory scene will be cluttered and confusing. Humans with normal hearing have the remarkable ability to perceptually integrate correlated sound waves. When the time interval between the direct wave coming from the source and a reflected wave of the source is sufficiently short, attributes of the delayed reflection are perceptually captured by the direct wave (Li et al., 2005), leading to a single fused image whose point of origin is perceived to be around the location of the leading source. This phenomenon is called "in human" (Wallach et al., 1949; for reviews see Li and Yue, 2002; Litovsky et al., 1999). Since a source is usually more correlated with its time-delayed reflections and less correlated (or uncorrelated) with other sources, the perceptual integration associated with the precedence effect facilitates perceived spatial segregation of signals from various sources. The precedence effect also occurs in various types of laboratory animals, including rats (Kelly, 1974; Hoeffding and Harrison, 1979).

In humans, the importance of perceptual fusion of correlated sound waves in improving recognition of speech signals against masking has been experimentally demonstrated (e.g., Freyman et al., 1999; Huang et al., 2008; Li et al., 2004; Rakerd et al., 2006; Wu et al., 2005). For example, when both the target and masker are presented by a loudspeaker to the listener's left and another loudspeaker to the listener's right, the perceived location of the target and that of the masker can be manipulated by changing the inter-loudspeaker interval for the target and that for the masker (Li et al., 2004). More specifically, for both the target and masker, when the sound onset of the right loudspeaker leads that of the left loudspeaker by a short time (e.g., 3 ms), both a single target image and a single masker image are perceived by the human listener as coming from the right loudspeaker. However, if the onset delay between the two loudspeakers is reversed only for the masker, the target is still perceived as coming from the right loudspeaker but the masker is perceived as coming from the left loudspeaker (Fig. 4). The perceived co-location and perceived separation are based on perceptual integration of correlated sound waves delivered from the two loudspeakers. It has been confirmed that perceived target–masker spatial separation facilitates the listener's selective attention to target signals and significantly improves recognition of target signals, even though neither the masker energy at each ear nor the stimulus-image compactness/diffusiveness is substantially changed (Li et al., 2004).

In rats, it has been recently discovered that compared to the precedence-effect-induced perceived co-location between the prepulse and noise masker, perceived spatial separation between the fear-conditioned prepulse and noise masker leads to significantly larger PPI in socially-reared rats (Du et al., 2009). Since the alteration between perceived co-location and perceived spatial separation between the prepulse and masker does not substantially change the signal-to-noise ratio at the ear, the perceived separation-induced PPI enhancement must involve higher-order central processes in improving the prepulse salience by facilitating selective attention to the prepulse signal. In other words, rats are

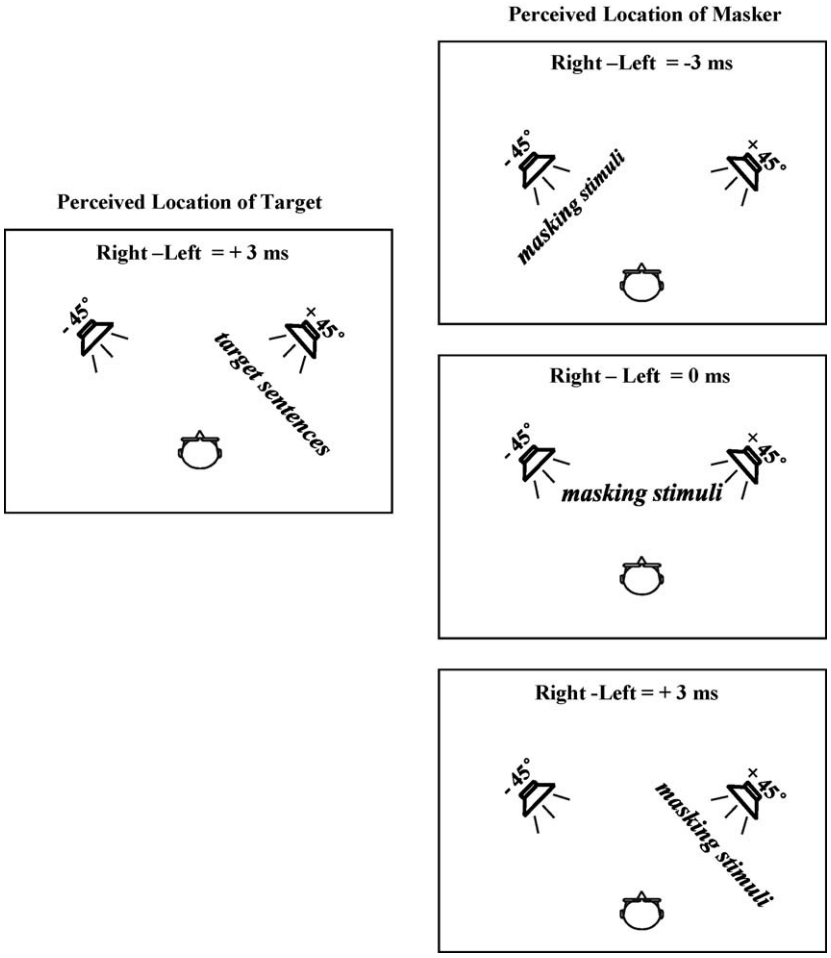

Fig. 4. Diagram showing the perceived locations of target stimuli and masking stimuli under different conditions. Both the target and masker are presented by each of the two loudspeakers with the separation angle of 90° in front of the listener. Under all conditions, the target delivered from the right loudspeaker leads that from the left loudspeaker by 3 ms (right − left = +3 ms, see the left panel), and the perceived location of the target is on the right due to the precedence effect. There were three perceived locations for the masking stimuli: (1) left, when the masker delivered from the right loudspeaker lags behind that from left loudspeaker by 3 ms (right − left = −3 ms, see the top-right panel), causing 90° perceived spatial separation between target and masker; (2) central, when the target delivered from the right loudspeaker starts simultaneously with that delivered from the left loudspeaker (right − left = 0 ms, see the middle-right panel), causing 45° perceived spatial separation between target and masker; (3) right, when the target delivered from the right loudspeaker leads that from the left loudspeaker by 3 ms (right − left = +3 ms, see the bottom-right panel), causing perceived co-location of target and masker. This figure was adapted from Li et al. (2004).

able to use the perceptual segregation between conditioned-prepulse image and masker image to facilitate attention to the prepulse signal, leading to enhanced PPI. However, if the prepulse is not fear conditioned, due to the lack of ecological value of the prepulse, it does not attract rats' selective attention even though perceived spatial separation between the prepulse and masker can be experienced by rats. Thus this new model using perceived spatial separation is particularly useful for studying attentional modulation of PPI in rats.

8. Mechanisms underlying conditional enhancement of PPI in laboratory rats

In rats, the amygdala is involved in modulating PPI (Decker et al., 1995; Fendt et al., 2000; Stevenson and Gratton, 2004; Wan and Swerdlow, 1997; for reviews see Li and Shao, 2003; Swerdlow et al., 2001). The amygdala, especially the lateral nucleus (LA), plays a critical role in forming fear conditioning (Fendt, 2001; Goosens and Maren, 2001; Maren, 1996; Romanski and LeDoux, 1992). Also, to mediate fear-related selective attention to the most salient signal and ignore other signals that emerge simultaneously, the amygdala is crucial for disrupting simultaneous temporal processing of two or more signals under stressful conditions in rats (Meck and MacDonald, 2007). Thus the fear-conditioning-induced enhancement of PPI may involve the amygdala. Since Group I metabotropic glutamate receptors subtype 5 (mGluR5) in the amygdala are essential for both the formation of fear conditioning (Fendt and Schmid, 2002; Rodrigues et al., 2002) and the formation of long-term potentiation in the amygdala (Lee et al., 2002; Rodrigues et al., 2002; Zheng et al., 2008), it is predicted that blocking mGluR5 should disrupt the conditioning-induced PPI enhancement. Indeed, before fear conditioning of the prepulse, systemic injection of the selective antagonist of mGluR5, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), markedly blocks the enhancing effect of fear conditioning on PPI (Li et al., 2008; Zou et al., 2007). Thus mGluR5 play a role in preserving the fear-conditioning-induced PPI enhancement. However, it is still not clear how the amygdala exerts its influences to the PPI circuitry to participate in modulation of PPI. Although the DpSC (one of the midbrain structures in the circuitry mediating PPI) receive direct axonal projections from the amygdala (Meloni and Davis, 2007) (Fig. 2), whether the descending projections play a role in mediating fear-conditional modulation of PPI still needs further investigation.

Moreover, the IC is the critical structure mediating acoustic PPI (Leitner and Cohen, 1985; Li et al., 1998a,b) and fear/anxiety states

(Brandao et al., 2003). Top–down modulations of auditory responses in the IC may play a role in modulating PPI. In humans, wave V of the brainstem auditory evoked potentials (BAEP) is mainly generated by the termination of the lateral lemniscus in the IC (Möller et al., 1994). Baas et al. (2006) reported that the amplitude of wave V of BAEP to clicks was increased by listeners' anticipation to electrical shock. Although the authors suggested that the increased amplitude of wave V under the shock threat reflects the descending influence from the amygdala, it is not clear whether there are direct axonal projections from the amygdala to the IC. To our knowledge, only one study reported that in both mustached bats (*Pteronotus parnellii*) and pallid bats (*Antrozous pallidus*) the basal amygdala (the magnocellular subdivision of the basal nucleus) sent a direct, widespread projection to the IC (Marsh et al., 2002). However, the function of this amygdalocollicular pathway in bats is still not clear. Thus in the future the mechanism underlying amygdaloid modulation of PPI needs further investigation.

It has been reported that the lateral globus pallidus projects to the PPTg (Takahashi et al., 2007) and the auditory cortex projects to the IC (Herbert et al., 1991) (Fig. 2). It is of interest to know whether these two descending pathways are necessary to top–down modulation of PPI.

9. PPI-modulation deficits in schizophrenic patients and ADHD patients

Schizophrenic patients usually have the difficulty suppressing irrelevant sensory stimuli to ensure processing of useful signals (for reviews see Braff et al., 2001; Geyer et al., 2001). Braff et al. (1978, 1992) first reported the PPI deficiency in schizophrenic patients. Their results show that compared to normal participants, schizophrenic patients exhibited significant PPI deficits at 60 and 120 ms intervals between the prepulse stimulus and startling stimulus. Their later studies support the results and further show that disruption of PPI is related to several typical positive or negative symptoms in schizophrenic patients (Braff et al., 1999; Perry and Braff, 1994). So far, numerous studies have confirmed the PPI deficiency in schizophrenic patients and schizotypal personality-disordered subjects (e.g., Cadenhead et al., 2000; Dawson et al., 2000; Evans et al., 2005; Kumari et al., 1999, 2000; Parwani et al., 2000; Swerdlow et al., 2006), and antipsychotic drugs can not only attenuate symptoms of schizophrenia but also reduce the PPI deficiency (Kumari et al., 1999, 2000; Weike et al., 2000; for reviews see Geyer et al., 2001; Hamm et al., 2001). However, medicated schizophrenic patients still exhibit approximately 20% less PPI than healthy controls (for reviews see Braff et al., 2001; Hamm et al., 2001). In addition, the magnitude of PPI in asymptomatic patients of schizophrenia is not significantly smaller than that in healthy controls when no explicit task regarding the processing of the prepulse is introduced (Kumari et al., 2000; Weike et al., 2000). Thus whether the PPI deficiency itself is specifically associated with certain symptoms of schizophrenia is still questionable.

When instructed to selectively attend to the prepulse stimulus, compared to normal controls, schizophrenic patients and schizotypal personality-disordered subjects exhibit not only reduced baseline PPI but also declined attentional modulation of PPI (e.g., Dawson et al., 1993, 2000; Hazlett et al., 1998, 2003, 2007; McDowd et al., 1993). For example, McDowd et al. (1993) examined PPI in both passive and active attentional paradigms within the same schizophrenic patients and found that the patients showed less PPI particularly in the active attention phase. In addition, Dawson et al. (2000) reported that in patients with schizophrenia under the condition when the prepulse was attended but not the condition when the prepulse was ignored, impaired prepulse inhibition was significantly correlated with heightened delusions, conceptual disorganization, and suspiciousness as measured with the expanded Brief Psychiatric Rating Scale. Thus Dawson et al. (2000) proposed that impaired attentional modulation of PPI reflects basic neurocognitive processes related to thought disorder in schizophrenia. Moreover, some recent studies have confirmed that the PPI deficiency that occurs when the prepulse is attended is more associated with the symptom severity in the schizophrenia spectrum (Hazlett et al., 2007) and the correlates between symptoms and PPI deficits in patients with schizophrenia cannot be detected in the passive-attention PPI paradigm (Swerdlow et al., 2006). Thus in patients with schizophrenia, the disability to focus on what is important (i.e., attentional deficits) can be reflected by deficient attentional modulation of PPI. As attentional deficits are the key features of schizophrenia, the impaired attentional modulation of PPI is more specifically correlated with the symptom severity of the disease than impaired baseline PPI.

In boys with attention-deficit/hyperactivity disorder (ADHD), PPI was reduced 120 ms after onset of the attended prepulse (Hawk et al., 2003), but unaffected if the boys were instructed to ignore the prepulse (Hawk et al., 2003) or PPI was tested with a no-task paradigm (Ornitz et al., 1992). Although diminished attention in patients with ADHD is an interesting issue that is worth further investigation using PPI paradigms under task-relevant, irrelevant, and no-task conditions with within-subject designs, up to date, there have been a very small number of published full-length reports (in primary journals) addressing attentional modulation of PPI in patients with ADHD. Thus it is impossible for us to provide an extensive review of this line of research.

Although both schizophrenic patients and ADHD patients exhibit deficient attentional modulation of PPI, their attentional deficits are fundamentally different in some perspectives. For example, Egeland (2007) has reported that patients with ADHD typically displayed a lethargic inattention characterized by high fatigue or a hyperactive-impulsive pattern and mainly suffered from deficient sustained attention over time, while patients with schizophrenia showed an inability to initially focus attention on current tasks. Clearly, there is a need to further develop paradigms specifically for testing different aspects of attentional modulation of PPI, such as those for differentiating the attention-initiation nature from the attention-maintenance nature of attentional modulation.

10. New animal models for studying schizophrenia

The neurodevelopmental hypothesis of schizophrenia emphasizes that certain early-life environmental factors have substantial influences upon the processes of brain maturation, and cause anatomical and functional abnormalities in the central nervous system (e.g., Ellenbroek and Cools, 1998; Marenco and Weinberger, 2000; McGrath et al., 2003; Meyer et al., 2005; Rehn and Rees, 2005; Weinberger, 1996). Therefore, several animal models involving early-life manipulations are proposed. One of the early-life manipulations is isolation rearing after weaning (21 days after birth in rats) (for a review see Weiss and Feldon, 2001). Isolation rearing results in substantial changes in both neural structures/neurotransmissions (Dalley et al., 2002; Day-Wilson et al., 2006; Harte et al., 2004; Heidbreder et al., 2000, 2001; Jones et al., 1991, 1992; Lapiz et al., 2000; Muchimapura et al., 2003; Preece et al., 2004; Whitaker-Azmitia et al., 2000) and behavior/cognition (Arakawa, 2005; Geyer et al., 1993; Jones et al., 1991; Li et al., 2007a; Paulus et al., 1998; Reboucas and Schimidek, 1997; Varty et al., 2000; Weiss et al., 2001; Wilkinson et al., 1994). PPI deficits in rats can be induced by early maternal separations or social isolation (Bakshi et al., 1998; Cilia et al., 2001, 2005; Li et al., 2008), and the deficits can be attenuated by both typical and atypical antipsychotics (Bakshi et al., 1998; Cilia et al., 2001, 2005; for reviews see Braff et al., 2001; Geyer et al., 2001; Weiss and Feldon, 2001).

It has been suggested that dysfunction of emotional brain systems is even more important in understanding schizophrenia, and both the central and basolateral nuclei of the amygdala contribute to this neurocognitive disorder (e.g., Aleman and Kahn, 2005; Shayegan and Stahl, 2005). Social isolation results in significant neurotransmission abnormalities in the rat's amygdala, including increased dopamine D-2 receptor density in the central nucleus of amygdala and reduced Fos-like immunoreactivity in the central and basolateral nuclei (Djouma et al., 2006; Muchimapura et al., 2002).

On the other hand, the prefrontal cortex, which is typically implicated in schizophrenia, reaches its anatomical and functional maturity only in early adulthood. Based on the postulation by Weinberger (1987), if early neurological injuries in the prefrontal cortex occur before the prefrontal maturity, the effects of the injuries may remain silent until the prefrontal cortex matures. In rats, the medial prefrontal cortex participates in the formation of fear conditioning (Baeg et al., 2001; Corcoran and Quirk, 2007) and attentional control (e.g., Wall and Messier, 2001), and projects to the amygdala (Freedman et al., 2000; McDonald et al., 1996; Sesack et al., 1989). Melendez et al. (2004) reported that the capacity of Group I mGluRs (mGluR1 and mGluR5) to elevate extracellular glutamate levels significantly decreased in the prefrontal cortex of isolation-reared rats compared to rats reared in normal environmental conditions.

We recently reported that a temporally precise combination of footshock with the prepulse stimulus significantly enhances PPI in socially-reared rats (Du et al., 2009; Huang et al., 2007; Li et al., 2008; Zou et al., 2007) and the fear-conditioning-induced PPI enhancement depends on activity of mGluR5 (Li et al., 2008; Zou et al., 2007). However, isolation rearing markedly impairs both the baseline PPI and the conditioning-induced PPI enhancement (Du et al., 2009; Li et al., 2008).

Particularly, the PPI enhancement induced by perceived spatial separation between the prepulse and noise masker disappears in rats with isolation rearing (Du et al., 2009). Thus even after the prepulse becomes fear conditioned (ecologically significant), due to the impairment of inhibitory control in attentional selection caused by isolation rearing (McLean et al., in press; Schrijver and Würbel, 2001), isolation-reared rats may not be able to efficiently inhibit the disruptive influence from the noise masker and shift selective attention to the location of the loudspeaker with the more salient prepulse image.

It is assumed that the impairment of fear-conditioning-induced PPI enhancement in isolation-reared rats is caused by certain anatomical and functional abnormalities in the cortico-striatal-pallido-thalamic circuitry including the amygdala, leading to that isolation-reared rats are not able to selectively attend to ecologically important sensory signals for a sufficiently long time when the disruptive startling stimulus is presented. Since higher-order central processes are involved in the PPI enhancement induced by either fear conditioning or perceived spatial separation and fear conditioning depends on activity of mGluR5, which contribute to glutamatergic dysfunction observed in patients of schizophrenia (Bach et al., 2007; Gupta et al., 2005; Pietraszek et al., 2007), the impairment of the conditional and/or perceptual modulation of PPI in isolation-reared rats must be useful for establishing new animal models for studying both cognitive features and biological bases of schizophrenia.

11. Animal PPI models for studying ADHD

Spontaneously hypertensive rats (SHR) have been widely used as animal models for studying ADHD (Sagvolden et al., 1992; for a recent review see Russell, 2007). The van den Buuse study (2004) reported that PPI in SHR was similar to that in age- and gender-matched genetic control Wistar–Kyoto rats (WKY) but "tended to be" higher than that in Sprague-Dawley rats ($P = 0.051$) when the prepulse level was 2, 4, 8, 12, or 16 dB over the 70-dB background. However, the Li et al. study (2007b) reported that although at the lower prepulse stimulus level (3, 6, or 9 dB above the 70-dB background) there were no differences between SHR and WKY, SHR showed profound PPI deficits compared to WKY at higher prepulse levels (12 or 15 dB above the background). Thus more studies are needed to clarity whether PPI is impaired in ADHD-modeling rats. Particularly, whether isolation rearing affects SHR and other strains' behaviors differently is still not very clear (but see Hunziker et al., 1996).

As mentioned before, in isolation-reared rats, both baseline PPI and conditional modulation of PPI are impaired. However, Hawk et al. (2003) reported that PPI diminished in ADHD boys only when the prepulse was attended. Thus, whether isolation rearing is suitable for studying ADHD is still an unsolved issue. Up to date, we have not seen any studies suggesting that isolation rearing can be used for establishing animal models of ADHD. Thus caution is needed about using isolation rearing for studying ADHD.

12. Conclusions and future directions

(1) This review indicates that PPI, which reflects the fast, early-stage gating processing, can be modulated by higher-order cognitive processes in both humans and rats. Up to date, the behavioral paradigms used for studying attentional modulation of PPI in humans are much better established than those in laboratory animals. Thus a critical issue in future research is how to establish PPI paradigms for rats using intermixed fear-conditioned prepulses and conditioning-controlled prepulses with a within-participant design. New animal PPI models are essential not only for examining effects of selective attention on PPI but also for encouraging related anatomical, pharmacological, and physiological studies.

(2) Although using the fMRI methods in human PPI studies has opened a new avenue in this line of research, the separation of the biological correlates for sensory coding from those for sensory gating is still facing a considerable hurdle. Also, since both prepulse and startling pulse elicit both sensory coding and sensory gating, the separation of the consequences of these two types of stimulation is a challenge in the brain-imaging approach.

(3) Improving the specificity to schizophrenia is the central issue in establishing animal models for studying this psychiatric disorder. Impairment of attentional modulation of PPI in isolation-reared rats may be used for boosting the generation of the new models for studying schizophrenia. Since attention-deficit is one of the major symptoms of ADHD, whether attentional modulation of PPI in rats can be used for studying ADHD is a new issue in future investigation.

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