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Review

# Prepulse inhibition in psychiatric disorders – Apart from schizophrenia

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ABSTRACT

Prepulse inhibition (PPI) is a robust operational measure of sensorimotor gating. In schizophrenic patients PPI is deficient. The aim of our review was to investigate the state of science regarding PPI and psychiatric disorders aside from schizophrenia. We used the online database PubMed in order to search for original published reports on PPI studies. The terms "prepulse inhibition", "sensorimotor gating", "blink recovery", and "blink reflex excitability" have been combined with the names of psychiatric disorders. We found that PPI is deficient in obsessive compulsive disorder (OCD) and Gilles de la Tourette's syndrome (GTS). In bipolar disorder dysfunctional PPI seems to be rather state dependent. Studies on depression and attention deficit/hyperactivity disorder (ADHD) consistently report no alterations. Evidence regarding sensorimotor gating in anxiety, autism, fragile X syndrome, posttraumatic stress disorder (PTSD), substance disorders, and Huntington's disease is still poor. There is a strong need for further studies on PPI in psychiatric disorders. PPI is highly applicable for translational research and might also be a very useful tool to investigate the mode of action of innovative, neuro-modulative techniques. Future PPI studies should control for influencing variables such as smoking, sex, or medication.



## 1. Introduction

The startle reflex is a primitive and protective body response to sudden and intense stimuli (Swerdlow et al., 1999). Prepulse inhibition (PPI) is an attenuation of the startle reflex when the startle-eliciting stimulus, the pulse, is preceded by a weaker sensory stimulus, the prepulse (*see* Fig. 1) (Graham, 1975). PPI is a robust experimental phenomenon, but even in healthy control subjects, the amount of inhibition of the startle reflex largely depends on prepulse and pulse characteristics, such as the pulse and prepulse intensity (Blumenthal, 1996) or prepulse to pulse interval (Blumenthal, 1999). Additionally, many studies report significantly reduced PPI values in patients with psychiatric disorders compared to healthy controls.

In 1975 Graham presumed that PPI is a fully automatic process. Nowadays the general view is that PPI depends highly on the experimental design and instructions given, whether automatic processes solely regulate PPI and whether attentional modulation intervenes. At short lead intervals (<60 ms), PPI relies mainly on automatic (preattentive) mechanisms (Dawson et al., 1993). Postma et al. demonstrated that subjects were able to detect prepulses at a rate of 51% when using an inter stimulus interval (ISI) of 40 ms between prepulse and pulse (Postma et al., 2001). However, there were no differences in the amount of PPI between trials in which prepulses were detected and when they were not. Since PPI occurs also in trials where the subject is only aware of one stimulus, a preconscious process can be assumed. In experimental settings, with longer inter stimulus intervals (120–240 ms), attentional modulation of PPI is possible by instructing subjects to focus or ignore the prepulse only, or both prepulse and pulse (Heekeren et al., 2004b; Swerdlow et al., 2001a).

The protection of processing hypothesis suggests that the prepulse activates preattentive mechanisms which inhibit pulse processing, to buffer sensory processing and to prevent an inundation of information (Graham, 1975; Norris and Blumenthal, 1996). PPI is a well established operational measure of sensorimotor gating (Li et al., 2009). The use of PPI in animal studies have made it possible to identify the underlying neuronal brain circuitries and to use PPI as a tool for fundamental research. PPI's advantages include: (i), It is a very applicable paradigm for translational research as PPI occurs in all mammals and primates, as well as in humans (Swerdlow et al., 1999); (ii) minimal compliance and low motivation of the subject are sufficient in order to conduct the measurement; (iii) the startle

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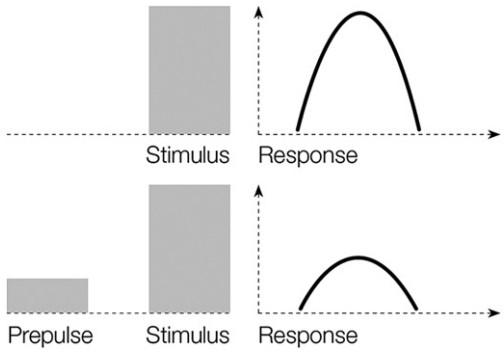


**Fig. 1.** Prepulse inhibition of the startle response.

response is sensitive to sensory, cognitive (Schell et al., 2000) and pharmacological manipulations and thus can be used in a wide variety of research studies.

In humans, the eye blink component of the startle reflex is most frequently measured and acoustic stimuli is also prevalently used. But PPI also occurs with visual and cutaneous stimuli and even occurs in cross modal paradigms (Swerdlow et al., 1999). In contrast to the whole body startle measurement in animals (like rodents), in humans, the Electromyography (EMG) records the electrical activity of the orbicularis oculi muscle to determine the magnitude of the reaction to the pulse. On the basis of the response amplitude in prepulse trials compared to pulse alone trials, the PPI value can be calculated. The PPI value, specified in percentages, is the primary outcome parameter but most studies also report the response latency and habituation rate. In acoustic paradigms, commonly used prepulse levels vary between 4 dB and 16 dB above background noise and startle eliciting pulses usually lie between 105 and 115 dB (Leumann et al., 2001).

### 1.1. The neural basis of PPI

In the early 1980's, Davis and his colleagues (Davis et al., 1982) published data from extensive work on the primary acoustic startle reflex (ASR) and its neural basis. By means of lesion and stimulation animal studies they showed that the ASR is mainly based on a four-step process (*see* Fig. 2). The acoustic input enters the cochlear nuclei (dorsal cochlea nucleus (DCN), cochlear root nucleus (CRN) and ventral cochlear nucleus (VCN)) that are part of the primary auditory pathway. Only if a certain threshold of stimulus intensity is exceeded (>80 dB), does the information pass on to the ventrolateral tegmental nucleus (VTN) and more importantly, to the caudal pontine reticular nucleus (PnC). The PnC is one of the lower brainstem nuclei and has direct projections to the motor neurons and seems to be a crucial element in the primary startle reflex pathway (Bosch and Schmid, 2006). In the final step, the motor neurons give rise to the motor response, which completes the pathway of the ASR (Davis et al., 1982).

Koch and Schnitzler (1997) proposed that the PPI of auditory stimuli is triggered by excitatory input from the auditory pathway to the midbrain inferior colliculus (IC). The IC in turn activates the superior colliculus (SC), which has important projections to the pedunculopontine tegmental nucleus (PPTg) that inhibits the PnC. The inhibition of the PnC leads to a down regulation of the startle response, which results in the measurable PPI effect (*see* Fig. 2). Different lines of research demonstrate the involvement of the IC and SC. The IC seems to be particularly important for the suppression of acoustically triggered startle reflexes. Whereas the SC plays a decisive role in linking information from different sensory modalities, which might explain the irrelevance of prepulse and pulse modality congruence. It has been demonstrated that lesions, either of the IC (Leitner and Cohen, 1985) or of the SC (Fendt et al., 1994) attenuate the PPI effect. In 1993 Swerdlow and Geyer were the first who investigated effects of PPTg lesions on PPI. Results suggest that the PPTg might be even more important in the mediation of PPI than the two colliculi. Lesions that affect less than half of the PPTg already lead to a complete loss of PPI (Swerdlow and Geyer, 1993). In addition, Li and Yeomans (2000) demonstrated that stimulation of the PPTg is sufficient to actuate PPI. However, this is still a matter of debate as other experts disagree with Li and his colleagues (Leumann et al., 2001).

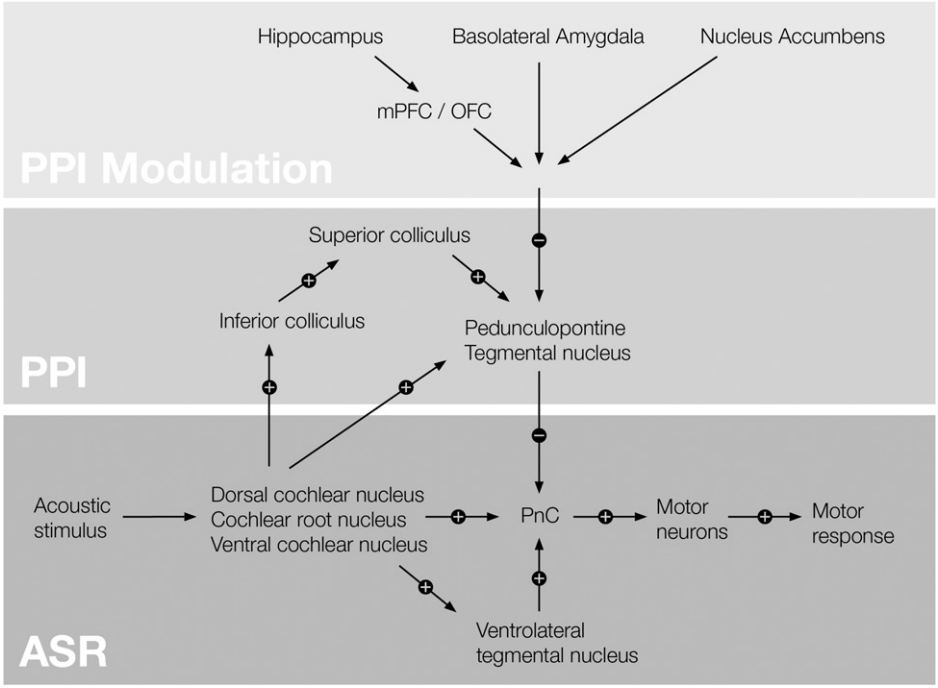


**Fig. 2.** Acoustic startle reflex (ASR) pathway, PPI circuit and its modulation.