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Prepulse inhibition of the startle reflex (PPI)

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Abstract

PPI is viewed as a functional measure of sensorimotor gating, a cognitive mechanism that helps exclude unnecessary sensory input, allowing for concentrated processing of relevant information. Impairments in PPI have been noted in several disorders, such as schizophrenia, OCD, alcohol dependence, Huntington's disease, and Alzheimer's disease. PPI has the potential to serve as an endophenotype for genetic studies and as a biomarker for assessing the effectiveness of treatments for neuropsychiatric conditions.

Introduction

Prepulse Inhibition (PPI) of the startle reflex refers to the phenomenon where a less intense, non-startling stimulus (prepulse) is delivered shortly before a startling stimulus (pulse), resulting in a reduced response to the startle. This reduction in the startle reflex is thought to symbolize a key form of sensorimotor gating, which allows for the filtering out of irrelevant or repetitive sensory information. PPI plays a protective role by reducing the disruptive effects that can interfere with the interpretation of prepulse signals. Impairments in PPI have been observed across various neuropsychiatric disorders, suggesting that PPI might serve as a biomarker for these conditions [4,13,24].

Sensorimotor gating mechanism

When a mild prepulse is presented before a startling stimulus, it activates neural pathways that diminish or lessen the startle reflex. Studies have confirmed the influence of top–down modulation of Prepulse Inhibition (PPI) in animals, as shown by the increase of PPI in rats following auditory fear conditioning and the observed difference between fear-conditioned prepulse and maskers. Considering that both baseline PPI and attentional modulation of PPI show deficits in individuals with schizophrenia, as well as the reduction of both baseline PPI and conditional modulation of PPI in rats raised in isolation, Liang and colleagues [16] highlighted the significance of investigating top–down modulation of PPI for creating new animal models to better understand the cognitive features and neural mechanisms underlying schizophrenia. The reduced PPI has been associated with impairments in central inhibitory systems that are crucial for attentional processes [19]. Neuroimaging studies suggest that PPI is related to activity in brain regions like the thalamus, striatum, hippocampus, and frontal cortex, which often show dysfunction in individuals with schizophrenia [12].

PPI is considered an operational measure of sensorimotor gating, which is a cognitive function that eliminates unimportant sensory information to enable concentrated processing of relevant data. The PPI of the startle response is an important indicator of deficits in information processing and failures in inhibition among individuals with schizophrenia. PPI is especially significant as it is consistently observed across all mammals, from humans to rodents. Deficits in Prepulse Inhibition (PPI) are noted across the "schizophrenia spectrum," impacting not only individuals diagnosed with schizophrenia but also their clinically unaffected family members. Simultaneous investigations employing both animal models and human brain imaging techniques have demonstrated that PPI is modulated by cortico-striato-pallido-thalamic (and pontine) circuitry, which is linked to the neuropathological and neurophysiological as-

pects of schizophrenia. The detection of PPI deficits in patients with schizophrenia has been validated by multiple research teams, with these deficits showing a correlation with markers of thought disorder and appearing to be "normalized" following treatment with Second-Generation Antipsychotic (SGA) medications. Consistent pharmacological impacts on PPI have been recorded; particularly, dopamine agonists induce PPI deficits, which are counteracted by both first-generation and SGA medications in animal studies. Furthermore, PPI exhibits considerable heritability in both human and animal populations, establishing it as a significant endophenotype for research involving families of schizophrenia patients. Genomic regions, including the NRGL-ERBB4 complex with its glutamatergic effects, are closely linked to PPI deficits in schizophrenia [3].

Startle reflex measurement

The startle reflex acts as a protective response initiated by a sudden and powerful stimulus, typically marked by a rapid blink and different physical reactions. The Acoustic Startle Reflex (ASR) can be easily accessed via electromyographic recordings in humans and large animals, as well as through whole-body movements in smaller animals like rodents, using a startle response system with a piezoelectric accelerometer placed under a platform to capture the related startle reactions. In humans, surface electromyographic activity has been recorded from various muscle groups throughout the body, showing variations in evoked responses between them [8].

PPI is typically evaluated by performing a set of experiments where a prepulse is shown before a pulse, and then the startle reaction, such as eye blink, is measured [2,14]. In 1982, Davis and associates identified a basic acoustic startle pathway in rats, consisting of the auditory nerve, the posteroventral cochlear nucleus, a nearby area to the ventrolateral lemniscus, the nucleus reticularis Pontis Caudalis (PnC), and spinal motoneurons. They proposed that a main acoustic startle pathway could involve three synapses that include cochlear root neurons, neurons in the PnC, and spinal motoneurons.

Clinical significance

Deficits in PPI have been observed in various conditions, including schizophrenia, OCD, alcohol, Huntington, and Alzheimer's disease.

Schizophrenia

The Phenomenon of Prepulse Inhibition (PPI) of the startle response is markedly diminished in individuals diagnosed with schizophrenia, signifying a disruption in sensory gating mechanisms. This impairment is believed to reflect neurobiological irregularities, particularly within dopaminergic and glutamatergic systems. Schizophrenia is linked to diminished inhibition. Research indicates that individuals experiencing their first episode of schizophrenia demonstrate lower PPI ratios compared to healthy subjects, suggesting impaired sensory gating [11,28]. PPI deficits continue beyond the acute phases of the disorder, implying that it may act as a reliable biomarker for schizophrenia [20]. Gaining insight into PPI deficits could aid in the formulation of targeted treatments addressing sensory processing challenges in schizophrenia [18]. Those with schizophrenia show significant PPI deficits, which are associated with the intensity of their symptoms and cognitive dysfunctions [15,26]. Patients with schizophrenia exhibit a Standardized Mean Difference (SMD) of -0.50 for PPI-60 and -0.44 for PPI-120, indicating considerable deficits [22]. Kumari and colleagues [13] discovered that an earlier onset of the illness correlated with decreased prepulse inhibition, whereas adult onset did not show this relationship. No significant correlations were found between current symptoms and prepulse inhibition. Patients treated with typical antipsychotics, in contrast to those receiving atypical medications, displayed lower prepulse inhibition when compared to healthy controls. Molina and colleagues [21] conducted a study involving 21 individuals with schizophrenia and 16 control subjects. After 21 days of quetiapine treatment, 17 patients were re-evaluated using PPI. The findings indicated that short-term treatment with quetiapine may not influence PPI measurements in individuals with schizophrenia.

On the other hand, while PPI serves as a valuable marker, it is crucial to acknowledge that not all individuals with schizophrenia display the same level of impairment, indicating variability in the expression of the disorder and its underlying mechanisms. This variability underscores the complexity of schizophrenia and the necessity for personalized strategies in treatment and research.

Other disorders

PPI deficits have been documented in conditions such as Obsessive-Compulsive Disorder (OCD), Tourette syndrome, Huntington's disease, and various other disorders [23]. The connection between the PPI of the startle reflex and OCD is intricate and has been investigated through numerous studies. Research findings suggest that although OCD is frequently linked with deficits in inhibition mechanisms, patients who are not on medication may not show the anticipated impairments in PPI of the startle reflex. Individuals with Tourette's syndrome and OCD also exhibit diminished PPI, reflecting a wider range of sensorimotor gating challenges [15]. A study involving 25 OCD patients who were not on medication revealed no significant deficits in PPI when compared to healthy controls, indicating that sensorimotor gating may not be uniformly compromised in OCD [6]. Notably, a subgroup of OCD patients categorized as 'checkers' showed heightened P50 suppression, suggesting possible differences in sensory processing among various OCD subtypes [6]. Furthermore, alcohol dependence has been associated with impaired PPI, indicating shared vulnerabilities in sensory processing across diverse psychiatric disorders [17]. The inhibition of the startle reflex by prepulses, especially in the context of Huntington's Disease (HD), is notably compromised due to degeneration in the striatum. This degeneration interferes with the typical sensorimotor gating process, which is crucial for suppressing involuntary reactions to unexpected stimuli. Individuals diagnosed with HD display significantly diminished Prepulse Inhibition (PPI), reflecting a severe impairment in their capacity to regulate the startle reflex. Compared to age-matched controls, HD patients demonstrate lower levels of PPI, irrespective of whether the startle response is initiated by auditory or tactile stimuli. Furthermore, stimuli that usually provoke maximal PPI in healthy subjects do not elicit the same response in patients with HD, highlighting the absence of normal modulatory influences from variations in prepulse intensity or timing [25].

Alzheimer's dementia

Research conducted on animals has revealed that the hippocampus and entorhinal cortex, which are impacted in mild Alzheimer's Disease (AD), play a role in the modulation of PPI. A study aimed to ascertain whether individuals with very mild AD exhibited changes in PPI and to explore potential relationships

between PPI and cognitive performance or neuropsychiatric symptoms. In this study a passive acoustic PPI paradigm was utilized involving 48 participants diagnosed with either mild AD or Mild Cognitive Impairment (MCI), alongside 49 healthy control subjects. No significant differences were observed in PPI between the patient group and the healthy controls. Additionally, PPI did not show any correlation with cognitive performance or neuropsychiatric symptoms. Given that mild AD is mainly characterized by a reduction in cholinergic markers within the limbic regions, this study implies that acetylcholine has a limited role in the regulation of PPI [10]. It has been proposed that startle PPI may serve as a biological marker for amnestic MCI and mild AD [27]; however, the impairments in PPI and sensorimotor gating have yet to be conclusively established [10]. The APOE ε4 allele is recognized as a significant risk factor for late-onset AD and has been demonstrated to be linked with startle response in APOE transgenic/knockout mouse models of AD [9]. Aziz [1] noted a considerable difference in PPI 120 when comparing cases to controls. Siblings exhibited behaviour that was intermediate between the two groups. Within the cases group, individuals lacking the APOE ε4 variant appeared to be more reactive than those possessing the APOE ε4 variant. The existence of the APOE ε4 variant has had a significant impact on both the onset and peak latency at ISI-120ms.

Conclusion

The startle reflex serves as a precise, reliable, reproducible, and non-invasive indicator of central nervous system function, utilized in a variety of research and clinical environments. The PPI can significantly enhance clinical investigations aimed at diagnosing psychiatric disorders. Additionally, it offers the benefit of being safe for participants and is relatively low-cost. A notable aspect of the startle response is its simple measurement, which reflects alterations in attentional processes and sensorimotor gating, both of which are influenced by psychiatric conditions [7]. The PPI has the potential to act as a biomarker in the early stages of psychiatric disorders and among first-degree relatives who are at an increased risk of developing the condition due to its objective nature and accurate assessment of sensorimotor gating and information processing, both of which are compromised in psychiatric illnesses. Furthermore, the PPI may represent a potential endophenotype for genetic research and serve as a biomarker to evaluate treatment efficacy for neuropsychiatric disorders.

Declarations

Transparency declaration: We confirm that the manuscript is an honest, accurate, and transparent account of the literature being reported.

Author contribution statement: The authors contributed to the writing up of the article and its review.

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