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Prepulse Inhibition of Startle Response: Recent Advances in Human Studies of Psychiatric Disease

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Prepulse inhibition (PPI) is considered to be one of the most promising neurophysiological indexes for translational research in psychiatry. Impairment of PPI has been reported in several psychiatric diseases, particularly schizophrenia, where PPI is considered a candidate intermediate phenotype (endophenotype) of the disease. Recent findings from a variety of research areas have provided important evidence regarding PPI impairment. Human brain imaging studies have demonstrated the involvement of the striatum, hippocampus, thalamus and frontal and parietal cortical regions in PPI. In addition, several genetic polymorphisms, including variations in the genes coding for Catechol O-methyltransferase, Neuregulin 1, nuclear factor kappa-B subunit 3 and serotonin-2A receptor were related to PPI; and these findings support PPI as a polygenetic trait that involves several neurotransmitter pathways. Early psychosis studies suggest that PPI disruption is present before the onset of psychosis. Also, discrepancy of PPI impairment between children and adults can be found in other psychiatric diseases, such as autistic spectrum disorders and posttraumatic stress disorder, and comprehensive investigation of startle response might contribute to understand the impairment of the neural circuitry in psychiatric diseases. Finally, recent studies with both Asian and Caucasian subjects indicate that patients with schizophrenia exhibit impaired PPI, and impaired sensorimotor gating might be a global common psychophysiological feature of schizophrenia. In conclusion, studies of PPI have successfully contributed to a better understanding of the fundamental neural mechanisms underlying sensorimotor gating and will certainly be most valuable in devising future approaches that aim to investigate the complex pathogenesis of psychiatric diseases.

KEY WORDS: Endophenotypes; Mental disorders; Psychophysiology; Schizophrenia; Startle reaction.

INTRODUCTION

To understand the complex pathogenesis of genetic and environmental interaction underlying psychiatric disease has been set as a critical goal, as hopes on translational research that combines both basic and clinical researchers have soared.

Prepulse inhibition (PPI) is considered to be one of the most promising neurophysiological indexes for translational research in psychiatry. Impairment of PPI is reported in several psychiatric diseases,[1)] of which schizophrenia is the most prominent. Other diseases include anxiety disorders, such as obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD), and developmental disorders, such as autistic spectrum disorders (ASD).

Although PPI is a well established index,[2-5)] there is still a vast number of research areas where the potential beneficial use of PPI has not been investigated. In this review, we briefly overview the well described applications of PPI and then discuss some recent advances in human PPI studies, including research on brain imaging, genetic analyses and comparison of PPI in different populations, at different ages.

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A BRIEF OVERVIEW OF PPI IN HUMAN SUBJECTS

PPI is usually defined as a reduction of the startle reflex due to weak sensory prestimulation.[6] PPI is considered to be the most common psychophysiological index of sensorimotor gating, which is an autonomic inhibition system that regulates sensory input by filtering out irrelevant or distracting stimuli. This prevents overflow of sensory information and allows for the selective and efficient processing of relevant information.[6-8] PPI is elicited by any kind of stimuli, including visual, acoustic, tactile or olfactory stimuli. Acoustic stimuli are usually used for experiments, and the majority of human studies measure orbicularis oculi muscle electromyographic activity of blink reflex induced by acoustic startle stimuli.[9] As PPI can be assessed using simple nonlinguistic stimuli, PPI is widely investigated across races[10-12] and species (animals,[3-5,13-15] such as rats or mouse), using similar experimental paradigms.

Although PPI is considered to be a stable index of individual sensorimotor gating,[16] several factors can affect its measurement. Some of the most relevant include gender, smoking and medication, in particular antipsychotic medication. Gender-related differences in PPI have been reported in normal subjects, with levels of PPI in women lower than in men.[17-24] In addition, women present fluctuations of PPI across the menstrual cycle,[25] with the lowest levels manifested in the mid-luteal phase.[18] PPI can also be enhanced by smoking[26-29]; however, this effect appears to be of short term duration (less than 10 minutes).[21] Some studies also reported the effects of substances such as caffeine,[30,31] cannabis,[32,33] and amphetamines,[34,35] on PPI. Finally, PPI is considered to be affected by the medication status and to involve several neurotransmitter pathways,[2,36-39] including the dopaminergic, glutamatergic, serotonergic and cholinergic pathways. This will be a matter of further discussion in the following sections.

PPI IN SCHIZOPHRENIA

Schizophrenia is one of the most prominent psychiatric diseases presenting deficits in PPI. Impaired sensorimotor gating has been considered to be a common psychophysiological feature of schizophrenia that may, theoretically, lead to severe dysfunctions in perception, attention and thinking.[40,41] Since Braff *et al*.[6] reported PPI reduction in schizophrenic patients, that reductions of PPI have been consistently demonstrated in schizophrenia.[2,38,42]

Recently, PPI has been considered a promising candidate intermediate phenotype (endophenotype) of schizophrenia.[43-46] PPI is not only reduced in schizophrenia patients but also in unaffected relatives,[47,48] and it has showed substantial heritability of 32-50%.[45,49,50] Deficient PPI has also been observed in patients with schizotypal personality disorder[47,51,52] and, to a lesser extent, in normal participants scoring high on psychometric measures of psychosis proneness.[53-55] Although the profile of startle measures is thought to differ across races,[10-12] patients with schizophrenia consistently had reduced PPI compared to normal controls in recent studies with Asian subjects.[56-58]

Numerous studies have provided evidence that PPI deficits in patients with schizophrenia are improved by antipsychotics,[24,37,38,40,42,59-67] in particular atypical antipsychotics, which appear to have a close association with PPI improvement in schizophrenia.[24,42,59-61,63,64,66,68-70] Although PPI has been reported in association with positive symptoms[65,71] and negative symptoms,[71,72] thought disorders[73] and social perception[74] of schizophrenia, most studies do not support a link between PPI and psychiatric symptoms.[24,63,70,75] However, this might be explained by the medication status of the patients, which is known to affect the relationship of psychiatric symptoms with PPI in schizophrenia.[76] While antipsychotic-naive schizophrenia patients[65,68,77-80] present PPI deficits, antipsychotic medication eliminates the impairment of PPI.[78,79] Vollenweider *et al*.[81] has suggested that clozapine enhances PPI in healthy humans with low but not with high PPI levels. On the other hand, haloperidol failed to increase PPI in subjects exhibiting low levels of PPI, despite the fact that PPI was attenuated in those subjects with high sensorimotor gating levels.[82] Therefore, the effect of antipsychotics on PPI might differ depending on the medication or the severity of the PPI deficits.[81,82] Longitudinal studies evaluating PPI before and after medication will help to elucidate the effect of antipsychotics on PPI in schizophrenia.

BRAIN AREAS INVOLVED IN PPI

In order to comprehend the physiological nature of PPI it is necessary to investigate the areas of the brain that are required during PPI. In experimental animals,[37,40,83] the cortico-striato-pallido-thalamic circuitry is thought to be responsible for modulation of PPI. A recent study[84] has shown that some forebrain areas are involved in top-down modulation of PPI. Recently, human brain imaging stud-

ies of PPI using several approaches, such as positron emission tomography and anatomical/functional magnetic resonance imaging (MRI), provided important evidence to understand the neurophysiological mechanisms of PPI.

The Kumari *et al*.[85] research group has published numerous important studies that addressed the biological nature of PPI. In an MRI volumetric voxel-based morphometry study, healthy subjects showed significant positive correlations between PPI and grey matter volume in the hippocampus extending to parahippocampal gyrus, basal ganglia, including parts of putamen, globus pallidus, and nucleus accumbens, superior temporal gyrus, thalamus, and inferior frontal gyrus. Patients with schizophrenia[86] showed significantly positive correlations between PPI and grey matter volume in the dorsolateral prefrontal, middle frontal and the orbital/medial prefrontal cortices. Functional MRI (fMRI) studies[87,88] showed that the PPI of healthy subjects was associated with increased activation in the striatum extending to hippocampus and thalamus, inferior frontal and inferior parietal regions, and that all activated regions had significantly greater response in healthy subjects than schizophrenic patients.[88] Patients treated with risperidone or olanzapine, but not with typical antipsychotics, showed significant activation in the PPI-relevant regions.[87]

Other research groups have found similar results. In an fMRI study of Campbell *et al*.,[89] PPI was found associated with activation in pons, thalamus, caudate nuclei, left angular gyrus and bilaterally in anterior cingulate. Also by fMRI, Hazlett *et al*.[90] showed that, using attend/ignore PPI paradigm, lower left caudate activation during the attended PPI condition was associated with more deficient sensorimotor gating among schizotypal personality disorder, schizophrenia, and healthy controls. In a PET[91] study, normal controls showed a positive association between PPI and metabolic activity rates of glucose in prefrontal (Brodmann's areas 8, 9, and 10 bilaterally) and lower in visual cortex, while patients only showed this association for area 10 in the left hemisphere.

These findings demonstrate the involvement of the striatum, hippocampus, thalamus, and frontal and parietal cortical regions in PPI. Dysfunctions in any of these regions may underlie observations of reduced PPI in psychiatric diseases, including schizophrenia, which might be improved by atypical antipsychotic medication.

GENETIC BASIS OF PPI

The use of PPI as an endophenotype in schizophrenia has been recently becoming consensual.[44,46,92] As PPI can be easily measured, it has the advantage to collect large sample sizes necessary for genetic approaches that conduct multi-site studies.[12] Several research groups have been investigating the relationship between PPI and the genome.

Roussos *et al*. and Giakoumaki *et al*.[93-96] have reported associations of PPI with several genotypes in healthy males. Examination of the Catechol O-methyltransferase (*COMT*) Val158Met polymorphism,[93] the main catabolic pathway of released dopamine (DA) in the prefrontal cortex (PFC), showed that Val (low PFC DA) /Val individuals had the lowest PPI, Met (high PFC DA)/Met the highest, and Val/Met were intermediate. In addition, the non-stimulant *COMT* inhibitor tolcapone increased PPI significantly in the Val/Val group and tended to have the opposite effect in the Met/Met group.[94] In a study examining the influence of the Dopamine D3 receptor Ser9Gly polymorphism on human PPI,[95] Gly/Gly individuals had the lowest PPI and Ser/Ser individuals had the highest PPI, while Ser/Gly individuals were intermediate. Investigation of the relationship between PPI and haplotypes comprising three Proline dehydrogenase (oxidase 1) single nucleotide polymorphisms (SNPs; 1945T/C, 1766A/G, 1852G/A) located in the 3' region of the gene,[96] CGA carriers, which are preferentially transmitted in schizophrenia patients,[97,98] exhibited attenuated PPI compared with the noncarriers. Furthermore, Roussos *et al*. examined the relevance for PPI of SNPs in promising schizophrenia risk genes, such as the D-amino acid oxidase (*DAO*) gene (rs4623951, rs2111902, rs3918346, rs3741775, and rs3825251)[99] and the Neuregulin 1 (*NRG1*) gene (rs6994992, SNP8NRG221132, SNP8NRG241930, rs3924999, rs2439272 and rs10503929),[100] and reported that reduced PPI was associated to the rs4623951_T-rs3741775_G and rs4623951_T-rs2111902_T diplotypes of *DAO* gene,[99] and to the SNP8NRG241930 G allele and particularly the rs6994992 T allele and rs2439272 C allele *NRG1* gene.[100]

The laboratory of Quednow *et al*.[101-103] has reported associations of PPI with several genotypes in both healthy subjects and patients with schizophrenia. An association of PPI with the serotonin-2A receptor (*5-HT_{2A}R*) A1438G/T102C (rs6311/rs6313), *COMT* Val158Met (rs4680) and *NRG1* Arg38Gln (rs3924999) were investigated in healthy Caucasian subjects,[101] and increased PPI levels were found in homozygous for the *5-HT_{2A}R* T102C-T/A-1438 G-A allele. Increased PPI levels were also found in male subjects with the *COMT* Met158Met-

genotype, but no significant association of PPI with the *NRG1* Arg38Gln genotype was detected. Investigation of the impact of three *5-HT$_{2A}$R* polymorphisms (A-1438G, T102C, H452Y) on PPI in Caucasian schizophrenia patients[102] showed that patients carrying the T102C TT and the A-1438G AA allele present significantly higher PPI levels compared with all other variants. In contrast, the H452Y polymorphism did not affect PPI. Quednow *et al*.[103] also investigated the impact of the *COMT* Val158Met polymorphisms on PPI in Caucasian schizophrenic inpatients, and reported that patients carrying the Met/Met allele showed elevated PPI levels compared to other two genotypes. PPI was also influenced by two common nicotinic acetylcholine receptor (nAChR) α3 subunit (*CHRNA3*) polymorphism (rs1051730/rs1317286) in healthy subjects and in patients with schizophrenia.[104] Recently,[105] the impact of the transcription factor 4 (TCF4) gene (rs9960767), a susceptibility gene for schizophrenia, on PPI was investigated in healthy subjects and in a schizophrenia spectrum group (including schizophrenia patients and individuals at high risk for schizophrenia), and in both samples PPI was strongly decreased in carriers of the schizophrenia risk allele C of the TCF4 gene.

Hong *et al*.[106] examined the effects of the *NRG1* Arg38Gln polymorphism on PPI in patients with schizophrenia and in normal controls. They reported that PPI was lowest in the subjects who were homozygous for the minor allele A/A carriers, intermediate in A/G carriers and highest in homozygous major alleles G/G carriers in both patient and control groups. Greenbaum *et al*.[107] reported an association of the reelin SNP rs7341475 with PPI. In addition, Hokyo *et al*.[108] reported that, in both healthy subjects and patients with schizophrenia, human N-methyl-D-aspartate (NMDA) receptor 2B subunit gene (*GRIN2B*) polymorphism rs1019385 (T200G) did not show any significant influence on PPI, although it was significantly related to habituation of startle response. Finally, Hashimoto *et al*.[109] reported that PPI deficits in schizophrenia were associated with PPI schizophrenia risk genotypes of three SNPs (rs11820062, rs2306365, rs7119750) in the v-rel avian reticuloendotheliosis viral oncogene homolog A gene, which encodes the major component of the Nuclear factor kappa B (NF-κB) complex.

All together, these data strongly support PPI as a polygenetic trait that involves several neurotransmitter pathways and the use of PPI as a valid schizophrenia endophenotype. However, as noted previously, PPI can be affected by several factors, such as gender, smoking status and antipsychotic medication, and future studies with large sample sizes that consider these effects are deemed required. Investigation of mechanism how these factors effect on PPI across genotypes will contribute to a better understanding of the fundamental neural mechanisms underlying sensorimotor gating and will certainly be most valuable in devising future approaches that aim to investigate the complex pathogenesis of psychiatric diseases.

EARLY PSYCHOSIS AND PPI

Research on early psychosis (ER) has been growing and PPI might also play an important role in this field.

In a 2-year follow-up study,[110] comparing ultra-high risk (UHR) adolescents with matched control group, UHR individuals showed reduced PPI at both baseline and 2 years compared with controls. Clinical improvement in UHR individuals was associated with an increase in PPI parameters. In another study,[111] PPI of acoustic startle response was assessed in subjects with prodromal symptoms of schizophrenia, first-episode schizophrenia patients and healthy control subjects. Prodromal subjects and unmedicated patients with first-episode schizophrenia showed significant PPI deficits, whereas schizophrenia patients treated with risperidone had almost normal PPI. These studies, together with the evidence that antipsychotic-naive schizophrenia patients[65,68,77-80] present PPI impairment, suggest that PPI disruption might be already present before the onset of psychosis and that PPI may represent a vulnerability marker for psychosis.

Intriguing results were found in a study[112] investigating PPI in EP, at risk (AR) for psychosis and comparison subjects at baseline and 6 months later. PPI was stable with repeated assessment and EP subjects had reduced PPI. The unexpected findings regard the fact that medication-naive EP subjects, as well as AR subjects who later developed psychosis, had greater PPI compared to EP subjects with antipsychotic medication, and to AR subjects who did not develop psychosis, respectively, introducing the possibility of early compensatory changes that diverge from findings in chronic patients. Therefore, longitudinal studies following up the pathological change of startle modulation in a long period prior to the onset of the disease are required to determine the use of PPI for early detection of psychosis.

PPI IN CHILDREN AND DEVELOPMENTAL DISORDERS

Startle modulation is not consistent through children to adults. The neurophysiological mechanisms of PPI are considered to undergo development during early childhood and do not mature until about 8 years of age in both male and female subjects.[113,114)]

Several studies have revealed PPI impairment in children with psychiatric disease, such as the 22q11 deletion syndrome,[115)] Tourette's syndrome[116)] and primary nocturnal enuresis.[117)] On the other hand, children with autism,[118,119)] attention deficit hyperactivity disorder (ADHD),[120,121)] PTSD,[122)] did not show PPI deficits (in traditional PPI experimental paradigm).

It should be noted that discrepancy in PPI between children and adults can be found in some psychiatric diseases. For instance, although children with autism did not[118,119)] show PPI deficits, adults with ASD, such as autism[123)] or Asperger's syndrome,[124)] presented PPI impairments. Adults with PTSD also exhibited PPI deficits,[125,126)] while children[122)] or adolescent[127)] with PTSD did not. The neurophysiological development related to PPI of startle response might not be relevant for some psychiatric diseases, such as ADHD, which did not exhibit PPI impairment in both children[120,121)] and adults,[128,129)] but might affect the discrepancy in PPI impairment between children and adults in other diseases, such as ASD or PTSD. Although PPI did not differ significantly between children with autism and normal age-matched controls, PPI of some controls were not evaluated, since they were rejected from the study for reasons such as drowsiness or small response.[119)] Patients with autism are known to have hyperacusia, and they might present a lower threshold of startle and elicit startle by weak stimuli which might not elicit startle in normal controls. It is important to determine an experimental paradigm which can assess sensorimotor gating in both children with ASD and typical development. Although PPI impairment is not apparent in children with autism, there might be deficits in the mechanism of startle response in children with ASD which would develop to PPI impairment when they become adults, and comprehensive investigation of startle response, including threshold to elicit startle, startle magnitude, as well as PPI, might contribute to uncover the impairment of the neural circuitry in autism. There are several attempts to develop experimental paradigm of PPI,[114,130-135)] including attentional modulation of PPI,[114,132-135)] and application of these paradigms might inform neurobiological basis underpinning PPI deficits in both children and adults with ASD.

CONCLUSION

PPI is a well-established neurophysiological index for translational research in psychiatric diseases. Recent studies from a variety of research areas all over the world have provided us important evidence to understand the neural mechanisms of sensorimotor gating, assessed by PPI. These findings will be most valuable in devising future studies that aim at investigating and understanding the complex pathogenesis of psychiatric diseases.

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