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# The Family of Sensorimotor Gating Disorders: Comorbidities or Diagnostic Overlaps?

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## Abstract

Prepulse inhibition (PPI) of startle is an operational measure of the pre-attentive filtering process known as sensorimotor gating. Originally identified in patients with schizophrenia, PPI deficits have been observed in multiple but not all psychiatric disorders. Thus, as with most signs and symptoms of psychiatric disorders, deficits in PPI cut across diagnostic categories. It remains unclear whether the diversity of disorders exhibiting deficient PPI bespeaks diagnostic overlaps or comorbidities. Given the recent focus on treatments for cognitive deficits of schizophrenia independently of treating psychosis, the relationship of PPI deficits to cognitive deficits becomes of interest. Although PPI cannot be considered to be a cognitive process per se, abnormalities in pre-attentive information processing may be predictive of or lead to complex cognitive deficits. Animal models of PPI deficits produced by dopamine agonists reliably predict existing antipsychotics. Nevertheless, since neither PPI nor cognitive deficits in schizophrenia are ameliorated by standard antipsychotics, current research is exploring the predictive value of non-dopaminergic PPI models in identifying treatments for gating disturbances independently of their relevance to specific disorders. Both PPI and cognitive deficits in schizophrenia patients are not reversed by first generation antipsychotics but may be attenuated by clozapine. Similarly, effects of glutamate antagonists on symptoms in patients and PPI in animals appear to be reduced by clozapine. Hence, treatment-induced reversals of deficits in PPI produced by glutamate antagonists may provide animal, and human, models to aid in the discovery of treatments of cognitive deficits in patients already treated with existing antipsychotics.

### Keywords

Prepulse inhibition; Schizophrenia; NMDA; Antipsychotics; MATRICS

## PREPULSE INHIBITION IN PATIENTS

### Gating Deficits in Schizophrenia

Measures of sensory or sensorimotor gating are among the most widely studied physiological markers used in laboratory studies of schizophrenia. For example, the auditory “sensory gating” paradigm pioneered by Freedman’s group involves a condition-test paired-stimulus paradigm in which the P50 event-related potential (ERP) elicited by the second of two audible clicks is normally reduced relative to the ERP elicited by the first click (Freedman *et al.*, 1999). In schizophrenia patients, however, this suppression of the P50 is diminished, apparently due to a reduction in short-term habituation. An analogous paradigm has been developed for use in rodents (Freedman *et al.*, 1999). This cross-species ERP paradigm has been critical in the identification of the alpha-7 nicotinic receptor as a potential target for pro-cognitive co-

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treatments in schizophrenia (Martin *et al.*, 2004). Another cross-species gating paradigm, prepulse inhibition of startle (PPI) is the focus of this review and differs qualitatively from the P50 ERP paradigm. Because it involves both sensory stimuli and motor responses (Graham, 1975), PPI is referred to as a measure of "sensorimotor gating" rather than sensory gating (Geyer and Braff, 1987; Braff and Geyer, 1990). In PPI, the acoustic startle response elicited by a sudden loud noise is measured in the presence or absence of a weak prepulse stimulus, which may be in the same or a different modality. The weak prepulse robustly inhibits the response to the subsequent startling stimulus. In contrast to P50 suppression, PPI is clearly not a form of habituation. In humans, startle is usually assessed via the eye-blink component of startle, using electromyography. In animals, the whole-body flinch aspect of the startle response is quantified using an accelerometer that is sensitive to dynamic movements. As first reported by Braff and colleagues in 1978 (Braff *et al.*, 1978) and confirmed in many subsequent reports (Braff *et al.*, 2001), PPI is reduced in schizophrenia patients. The early demonstrations of PPI deficits in schizophrenia were based on groups of patients who were, for the most part, treated with first generation or so-called typical antipsychotic drugs. More recent studies have demonstrated similar deficits even in first-break patients who had never been treated with any antipsychotics (Ludewig *et al.*, 2003). Thus, deficient PPI in schizophrenia is not attributable to medications or the course of illness, but it is also not reversed by first-generation antipsychotic treatments.

## Sensorimotor Gating Deficits in Psychiatric disorders

Studies of PPI as an operational measure of sensorimotor gating were originally intended to test the general theory that failures of inhibitory filtering mechanisms can lead to sensory overload and consequent cognitive fragmentation in schizophrenia (Geyer and Braff, 1987; Braff and Geyer, 1990). Nevertheless, subsequent research has demonstrated that PPI is reduced not only in schizophrenia but also in patients suffering from a variety of neuropsychiatric disorders characterized by deficits in the gating of motor, sensory, and/or cognitive information (Braff *et al.*, 2001). Thus, as reviewed in some detail in Braff *et al.* (2001), studies prior to 2001 demonstrated that PPI deficits are also evident in patients with schizotypal personality disorder, Obsessive Compulsive Disorder (OCD), Tourette's Syndrome, and Huntington's Disorder, and under some experimental conditions PTSD. This group of disorders has been suggested to reflect a family of disorders which can be characterized as having deficits in the gating of motor (Huntington's, Tourette's), sensory (schizophrenia), and/or cognitive information (OCD) (Braff *et al.*, 2001; Hoenig *et al.*, 2005). In addition, more recent studies have revealed similar deficits in PPI in another psychotic disorder, namely bipolar disorder patients, at least in the manic phase of the illness (Perry *et al.*, 2001). Bipolar disorder has long been conceptualized as including failure of motor inhibition. Adequate studies have not yet been reported to determine the extent to which these PPI deficits in bipolar disorder are state-related, and specific to the manic phase, or trait markers. One indication supporting the former possibility is the recent report that PPI is normal in effectively treated, non-manic patients with childhood bipolar disorder (Rich *et al.*, 2005). In additional studies prompted in part by suggested genetic contributions to schizophrenia or related disorders, deficits in PPI have also been identified in children with 22q deletion syndrome (Sobin *et al.*, 2005), young persons with Fragile X syndrome (Frankland *et al.*, 2004), and adults with Asperger's syndrome (McAlonan *et al.*, 2002), seizure disorder (Pouretemad *et al.*, 1998), or Lewy body dementia (Perriol *et al.*, 2005).

As the range of psychiatric disorders in which PPI has been examined has increased, further evidence has accrued to demonstrate that abnormalities in sensorimotor gating are largely independent of classical diagnostic categorizations. Within the family of anxiety disorders, one finds PPI deficits in panic disorder (Ludewig *et al.*, 2002). These deficits in panic disorder patients appear to be reduced though perhaps not abolished by standard clinical treatments

(Ludewig *et al.*, 2005). Panic Disorder can also be seen as one which patients suffer from impairments in inhibiting the processing of sensory and cognitive information related to anxiogenic stimuli. Similarly, boys diagnosed with attention-deficit hyperactivity disorder (ADHD) exhibit deficits in the attentional modulation of PPI, although they appear to be normal in the typical passive PPI paradigm used in most other studies (Hawk *et al.*, 2003). Furthermore, as appears to be the case in panic disorder, effective treatment of ADHD with methylphenidate reverses the attentional deficit seen in the PPI paradigm (Hawk *et al.*, 2003). It should also be noted, however, that deficient PPI is not found in several other psychiatric disorders, including Parkinson's disease (Perriol *et al.*, 2005), Alzheimer's disease (Hejl *et al.*, 2004; Perriol *et al.*, 2005), or unipolar depression (Ludewig and Ludewig, 2003; Perry *et al.*, 2004; Quednow *et al.*, 2004). Thus, deficits in PPI span a wide range of diagnostic categories, although some specificity is evident. The so-called family of psychiatric gating disorders can be seen to be consonant with the broad importance of behavioral inhibition, attention, and information processing to normal behavioral function. PPI appears to tap into fundamental aspects of inhibitory processing that are impacted in a variety of disease states. Such measures are in fact the most tractable to study in cross-species models relevant to psychiatric treatments (Geyer and Markou, 2002). One implication of this observation is that it may be fruitful to consider developing treatments that use PPI paradigms to develop treatments that would improve gating functions independently of broad diagnostic syndromes. Considering such a possibility is timely insofar as recent efforts have begun to establish opportunities for registration of compounds as treatments for specific aspects of complex psychiatric disorders such as schizophrenia, without requiring that these treatments affect the entire clinical syndrome.

## THE MATRICS PROGRAM

### The MATRICS Program to Develop Procognitive Treatments in Schizophrenia

For decades, the United States Food and Drug Administration (FDA) only licensed drugs for use in schizophrenia if they impacted positive psychotic symptoms. This constraint prevented the identification and development of novel treatments for the problems experienced by schizophrenia patients (Fenton *et al.*, 2003; Hyman and Fenton, 2003). Despite the many observations that specific signs and symptoms appear to transcend classical diagnostic categories, the FDA approach to psychiatric treatment has been to treat the entire disorder with one compound, rather than treat specific clinical problems with specific compounds. Clearly, cognitive deficits - which have been long recognized as being important aspects of schizophrenia - are not treated adequately, if at all, by current antipsychotic treatments (Green, 1996; Fenton *et al.*, 2003). Indeed, these cognitive deficits appear to contribute significantly to the poor functional outcome exhibited by schizophrenia patients treated with antipsychotics (Green *et al.*, 2004a). Thus, despite the plethora of existing antipsychotic treatments, the cognitive deficits remain as clinical problems in schizophrenia, and most patients cannot work effectively.

In response to the identification of the bottleneck limiting the development of treatments specifically directed at the cognitive deficits in schizophrenia, the U.S. National Institute of Mental Health (NIMH) developed the MATRICS Program. MATRICS - Measurement and Treatment Research to Improve Cognition in Schizophrenia - developed a broad consensus regarding the nature of the cognitive impairments in schizophrenia and how they might best be assessed and treated (Marder and Fenton, 2004). The MATRICS approach to the problem is to treat cognitive deficits and psychotic symptoms separately. Over a period of two years, MATRICS gathered the relevant stakeholders in both industry and academia to achieve a consensus and establish a clear path that would enable the FDA to consider registering compounds intended to treat cognitive deficits in schizophrenia, independently of treating psychosis *per se*. The paradigmatic use of such compounds would be as co-treatments in schizophrenia patients maintained on stable antipsychotic medications. Hence, these patients

would presumably exhibit few of the positive symptoms of schizophrenia that could complicate the assessment of cognitive deficits and impede the ability of patients to benefit from cognitive enhancers.

### The MATRICS Consensus Process

MATRICS consisted of a series of consensus conferences, each organized by an expert committee and listed on the MATRICS website (www.matrics.ucla.edu). First, the Neurocognition Committee identified the primary domains of cognitive deficits that characterize patients with schizophrenia: working memory; attention/vigilance; verbal learning and memory; visual learning and memory; speed of processing; reasoning and problem-solving; and social cognition (Nuechterlein *et al.*, 2004). Second, the Neuropharmacology Committee identified the most promising molecular targets, existing compounds, human test measures, and potentially useful animal models for use in the discovery of treatments that target basic mechanisms related to complex cognitive operations (Geyer and Tamminga, 2004). Third, a consensus process was used to develop recommendations for the appropriate cognitive tests to be used in clinical assessments of potential cognitive enhancers (Green *et al.*, 2004b). Fourth, a MATRICS conference examined ways to increase collaborations between NIMH and industry in order to support drug discovery and registration. Fifth, a joint meeting MATRICS meeting brought the FDA and NIMH together to address the processes needed for assessment of cognition as an endpoint in clinical trials (Buchanan *et al.*, 2005). Sixth and last, a concluding MATRICS meeting looked ahead toward a research agenda that would foster improved methods for the discovery, validation, and assessment of pro-cognitive co-treatments for schizophrenia (Geyer and Heinssen, 2005). Throughout the two-year process, the MATRICS conferences included participants from NIMH, NIH, FDA, as well as academic and industry representatives, and were very effective in establishing a broad consensus regarding the appropriate criteria and opportunities for discovering and evaluating co-treatments for the cognitive impairments in schizophrenia.

## PREPULSE INHIBITION MODELS IN ANIMALS

### Using Prepulse Inhibition for Drug Discovery

As a result of the MATRICS program, drug discovery in schizophrenia is now focused on the identification of potential pro-cognitive co-treatments. In the post-MATRICS era, the question arises as to the possible utility of PPI models in the discovery process for pro-cognitive co-treatments. Since the anticipated application is for co-treatments to be used in patients already stably treated with antipsychotic drugs, any animal model that is responsive to first-generation antipsychotics is likely to be uninformative. The fundamental difficulty in evaluating the potential applicability of animal models for the prediction of pro-cognitive agents in schizophrenia is the absence of any established positive control compound. That is, in the absence of any path to registration of pro-cognitive treatments that do not also treat positive symptoms of schizophrenia, virtually no studies have been done in this specific area (Floresco *et al.*, 2005). What we have some information about, however, are comparisons of different classes of antipsychotic drugs on both cognition and PPI in patients with schizophrenia. It is clear that first-generation antipsychotics, which are principally dopamine $D_2$ antagonists, have no beneficial effects on cognition (Hagan and Jones, 2005). Similarly, as evident from the many early demonstrations of deficient PPI in antipsychotic-treated patients, first-generation compounds do not normalize PPI in schizophrenia (Braff *et al.*, 2001; Kumari and Sharma, 2002). With respect to second-generation antipsychotics, and in particular clozapine, the evidence is less clear but indicates that clozapine and some other multi-receptor antagonist antipsychotics may help to improve cognition to some degree (Meltzer and McGurk, 1999) and appear to be associated with relatively normal PPI (Kumari and Sharma, 2002). Of particular interest in this regard is a cross-sectional study indicating that clozapine treatment,

relative to typical antipsychotic treatments, is associated with reduced PPI deficits in patients with schizophrenia (Kumari *et al.*, 1999). While the evidence indicating that second-generation antipsychotics, especially clozapine, may ameliorate PPI deficits in schizophrenia is based largely on cross-sectional studies (Kumari *et al.*, 1999; Hagan and Jones, 2005), some longitudinal studies are now suggesting that PPI deficits may be reversed in groups of schizophrenia patients treated primarily with second-generation compounds (Meincke *et al.*, 2004). Although much more work is needed to clarify the effects of newer antipsychotics on both cognitive and PPI deficits in schizophrenia, it is clear that first-generation anti-psychotics fail to normalize either class of deficits.

## NMDA Antagonist Effects in Humans

The original suggestion that glutamatergic systems may contribute to symptoms of schizophrenia, derived from the observation that *N*-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine or ketamine produce psychotic symptoms that resemble those seen in schizophrenia (Krystal *et al.*, 1994; Malhotra *et al.*, 1996; Vollenweider and Geyer, 2001). In contrast to effects produced by dopamine agonists such as amphetamine, which primarily resemble only the positive symptoms of schizophrenia, the effects of NMDA antagonists have been suggested to mimic the positive, negative, and cognitive symptoms of schizophrenia (Krystal *et al.*, 1994; Malhotra *et al.*, 1996; Vollenweider and Geyer, 2001; Geyer and Moghaddam, 2002). Further, administration of the NMDA receptor antagonist ketamine to schizophrenia patients exacerbates both psychotic symptoms and cognitive impairments (Malhotra *et al.*, 1997b). With respect to the cognitive deficits, it appears that, within groups of schizophrenia patients, the most robust correlates of the deficits in PPI are abnormalities in distractibility (Karper *et al.*, 1996) and thought disorder (Perry *et al.*, 1999). Importantly, there is strong evidence that the psychotomimetic effects of ketamine in humans are insensitive to first-generation antipsychotics such as haloperidol, but are reduced in patients treated with clozapine (Malhotra *et al.*, 1997a,b).

## Prepulse Inhibition Models in Rats

The cross-species nature of startle and PPI has aided the development of animal models of deficits that are extremely similar to the gating deficits seen in psychiatric disorders. By virtue of the historical focus on treating positive symptoms of psychosis in schizophrenia, most of the existing literature on uses of PPI in animal models has addressed the possible discovery of novel antipsychotic treatments. Given the presumed relevance of dopaminergic systems to schizophrenia, mania, and other psychiatric disorders, the earliest rodent models began with demonstrations of the ability of dopamine agonists to disrupt PPI in rats. Subsequently, the rat PPI models have evolved into at least four different models (Geyer *et al.*, 2001). These distinct models have PPI measures in common but are differentiated by the manipulations used to disrupt PPI: 1) psychostimulant dopamine agonists; 2) hallucinogenic serotonin agonists; 3) psychotomimetic NMDA receptor antagonists; and 4) developmental manipulations such as isolation rearing or neonatal lesions of the ventral hippocampus. Three of the models are based on changes induced by acutely administered psychotomimetic drugs. While pharmacological approaches that alter PPI help to identify relevant neural substrates, they do not assess environmental or developmental contributions to PPI deficits. In contrast, the fourth PPI model is based on the loss of PPI in adult rats subsequent to social isolation during development (Powell and Geyer, 2002). Although this isolation rearing model and other developmentally based models has proven to be of value in testing antipsychotic treatments (Pen and Moreau, 2002; Powell and Geyer, 2002; Cilia *et al.*, 2005), only the dopamine and NMDA models are particularly relevant for the present discussion.

## The Dopamine Prepulse Inhibition Model in Rats

As detailed in other reviews (Geyer *et al.*, 2001; Swerdlow *et al.*, 2001), PPI deficits that mimic those seen in schizophrenia were first produced in animals by the administration of direct or indirect dopamine agonists, such as apomorphine or d-amphetamine (Geyer *et al.*, 1990). The original dopamine model focused primarily on testing the ability of antipsychotic drugs to block the PPI-disruptive effects of apomorphine in rats (Swerdlow *et al.*, 1994). In sum, these effects of apomorphine in rats are reliably prevented by virtually all antipsychotics that have appreciable affinity for dopamine $D_2$ receptors. Swerdlow *et al.* (1994) have shown an excellent correlation between the clinical potency of an antipsychotic and its ability to block the PPI-disruptive effects of the dopamine agonist apomorphine in rats. Although this finding provides important validation of the predictive validity of the dopamine PPI model for antipsychotic drugs, it primarily reflects the importance of dopamine $D_2$ antagonism in antipsychotic drug action and therefore only recapitulates in a behavioral paradigm what was already known from simple ligand-binding assays. Thus, the dopamine agonist PPI model is an example of what we have called “receptor tautology”, given that the receptor mechanism of the agonist used to induce the schizophrenia-like PPI deficit predicts the antagonists that the behavioral test will identify. Furthermore, in the context of searching for pro-cognitive co-treatments to be added to stable regimens of current antipsychotics that have dopamine $D_2$ antagonist actions, any animal model based on $D_2$ agonist effects is clearly irrelevant.

In contrast to $D_2$ antagonist effects, manipulations of dopamine $D_1$ receptors was considered one of the most promising possible targets for pro-cognitive agents in schizophrenia by the MATRICS Neuropharmacology group (Goldman-Rakic *et al.*, 2004). The effects of dopamine agonists on PPI in rats are clearly due largely to actions at the dopamine $D_2$-family of receptors (Geyer *et al.*, 2001), which is quite consistent with the actions of existing antipsychotic drugs. Overall, $D_2$ agonists rather than $D_1$ agonists reduce PPI in rats, with the corresponding antagonists have the expected opposing effects. In addition, the effects of indirect releasers of dopamine, such as amphetamine or cocaine, also appear to disrupt PPI in rats via actions mediated at $D_2$-family receptors. Nevertheless, several reports have demonstrated important differences between rat strains in their sensitivity - or insensitivity - to the PPI-disruptive effects of dopamine agonists (Swerdlow *et al.*, 2000; Geyer *et al.*, 2001). Furthermore, recent studies by Swerdlow’s group have shown some important differences in the influences of direct $D_1$ and $D_2$ agonists in various rat strains, and have even demonstrated the heritability of some of these differences (Swerdlow *et al.*, 2006). In mice, the effects of dopaminergic manipulations on PPI are even more complex. In particular, the influences of dopamine $D_1$ receptors on PPI appear to be much more important in mice than in rats. Extensive studies with both selective antagonists and receptor subtype-specific knockout mice have demonstrated that the effects of amphetamine on PPI are attributable to actions at the $D_2$ subtype of the $D_2$-family of dopamine receptors, and not to $D_1$, $D_3$, or $D_4$ receptors (Ralph *et al.*, 1999; Ralph-Williams *et al.*, 2002). Similarly, the disruptions of PPI observed in dopamine transporter knockout mice, likely mediated indirectly via the increased synaptic levels of dopamine, are reversed by $D_2$ and not $D_1$ receptor antagonists (Ralph *et al.*, 2001). Nevertheless, in contrast to rats, $D_1$ agonists are much more effective than $D_2$ agonists in disrupting PPI in mice (Ralph-Williams *et al.*, 2002; 2003; Ralph and Caine, 2005). These effects of the direct $D_1$ agonists are prevented by $D_1$ and not $D_2$ antagonists (Ralph-Williams *et al.*, 2003) and are absent in $D_1$ but not in $D_2$ knockout mice (Ralph- Williams *et al.*, 2002). Thus, while indirect agonist effects on PPI in mice appear to be mediated similarly to those observed in mice, the actions of direct dopamine agonists in mice appear to differ from those in rats or, for that matter, from the effects of indirect dopamine agonists in mice. Clearly, more research is needed to clarify the sources of these surprising disparities.

Such disparities prompt considerations of which rodent literature is more relevant to the influences of dopamine receptors on PPI in humans, though adequate discussion of this issue is beyond the scope of this review. In brief, as summarized elsewhere (Swerdlow *et al.*, 2001; 2002), neither indirect dopamine agonists, such as amphetamine, nor direct dopamine $D_2$ agonists, such as bromocriptine, pergolide, or ropinirole, reliably disrupt PPI in humans. While the doses of dopamine agonists used in some studies may have been inadequate, even the effects of dopaminergic antagonists that have been observed in humans have not been readily replicated (*e.g.*, Abduljawad *et al.*, 1999). Furthermore, as noted above, PPI deficits in schizophrenia patients are clearly not reversed by even prolonged treatment with first-generation antipsychotic treatments having clear antagonist actions at $D_2$ dopamine receptors (Braff *et al.*, 2001). Since there is almost no evidence regarding the possible influences of dopamine $D_1$ receptor manipulations on PPI in humans, the potential relevance of the effectiveness of $D_1$ agonists and antagonists on measures of PPI in mice cannot yet be evaluated.

## The NMDA Antagonist Prepulse Inhibition Model

The rodent PPI model that shows the greatest potential to provide insight into the unique effects of second- rather than first-generation antipsychotics is the NMDA antagonist model. As reviewed elsewhere (Geyer *et al.*, 2001), both competitive and non-competitive NMDA antagonists (*e.g.*, phencyclidine, dizocilpine, and ketamine) produce robust deficits in PPI in rats, mice, or infra-human primates. In addition, the NMDA antagonist model appears to be the least sensitive of the existing rodent models to strain differences in the observed effects (Geyer *et al.*, 2001). Many studies of the effects of antipsychotics on the PPI-disruptive effects of NMDA antagonists have confirmed that first-generation antipsychotics such as haloperidol do not attenuate the PPI-disruptive effects of NMDA antagonists in rats (Geyer *et al.*, 1990; 2001). Similarly, the effects of NMDA antagonists on PPI are maintained in mice treated with dopamine antagonists or in mutant mice lacking specific subtypes of dopamine receptors (Geyer *et al.*, 2002; Ralph-Williams *et al.*, 2002). In contrast, clozapine and some other second-generation antipsychotics have been demonstrated to reduce the disruption in PPI produced by NMDA antagonists in both rats (Geyer *et al.*, 2001) and mice (Geyer *et al.*, 2002; Brody *et al.*, 2004). This interaction between clozapine and NMDA antagonists is seen only with a limited range of doses and has been confirmed in many but not all studies in rats (Geyer *et al.*, 2001). Complementing the studies in rodents, clozapine has been demonstrated to attenuate the effects of phencyclidine on PPI in monkeys, while haloperidol was ineffective (Linn *et al.*, 2003). These results in experimental animals are consistent with the human studies discussed above, indicating that the psychotic symptoms produced by NMDA antagonists are not reduced by typical antipsychotics but are blocked by clozapine (Malhotra *et al.*, 1997a,b). Such findings led to the suggestion that the phencyclidine-PPI model might enable the specific identification of atypical rather than typical antipsychotic treatments (Geyer and Ellenbroek, 2003).

There is some limited evidence that chronic treatments with relatively high doses of typical antipsychotics in rats can attenuate the effects of NMDA antagonists on PPI (Geyer *et al.*, 2001), in contrast to the ineffectiveness of acute administrations of these drugs. While further studies along these lines are clearly warranted, it should be noted that the antipsychotic effects of dopamine antagonists in patients appear to be evident even acutely and attributable to the same pharmacological actions that are responsible for the longer term further improvement in psychosis ratings seen with chronic antipsychotic administration. Thus, the use of acute treatments in predictive animal models is consistent with the clinical reality. Furthermore, the apparent effectiveness of chronic administrations of typical antipsychotics in the NMDA model is not corroborated by the studies of dopamine receptor knockout mice, which clearly

demonstrate that neither $D_1$ nor $D_2$ dopamine receptors are required for NMDA antagonists to disrupt PPI (Ralph-Williams *et al.*, 2002).

The interactions between second-generation antipsychotics and NMDA antagonists in PPI paradigms are unlikely to be mediated by competition for a common receptor, because antipsychotics do not have appreciable affinity for NMDA receptors. Rather, the reductions in NMDA antagonist-induced PPI deficits following clozapine-like antipsychotics likely reflect interactions within the complex forebrain circuitry that modulates PPI (Bakshi and Geyer, 1998; Swerdlow *et al.*, 2001). Thus, the NMDA antagonist PPI model does not appear to be another instance of receptor tautology and may, therefore, provide a pathway to identification of novel molecular targets for treatments of schizophrenia.

## CONCLUSIONS

Deficits in PPI were originally examined in patients with schizophrenia, testing the theory that gating deficits contribute to cognitive disorganization. Nevertheless, PPI deficits have been observed subsequently in multiple psychiatric disorders. Thus, as with most signs and symptoms of psychiatric disorders, deficits in PPI cut across diagnostic categories. It remains unclear whether the diversity of disorders exhibiting deficient PPI bespeaks diagnostic overlaps or comorbidities. Rather than focus on this question, many have argued that psychiatric treatments need to target specific components of illness rather than entire syndromes. Indeed, the PPI deficits in schizophrenia patients, like the cognitive deficits that are core features of schizophrenia, are not reversed by most antipsychotic drugs. Recently, the MATRICS program has fostered new approaches to develop treatments for cognitive deficits and other specific aspects of schizophrenia independently of treating psychosis. It appears that the cognitive deficits that are refractory to existing treatments represent a critical unmet treatment need. Accordingly, the possible relationship of PPI deficits to cognitive deficits is of current interest in both human and animal studies. Although PPI cannot be considered to be a cognitive process *per se*, abnormalities in pre-attentive information processing may be predictive of or even lead to complex cognitive deficits. Animal models of PPI deficits produced by dopamine agonists reliably predict existing antipsychotics. Given that the patients will already be treated with antipsychotics having antagonist actions at dopamine $D_2$ receptors, however, dopamine agonist models are inappropriate for use in identifying pro-cognitive co-treatments in schizophrenia. Since neither PPI nor cognitive deficits in schizophrenia are ameliorated by most existing antipsychotics, current research is exploring the predictive value of non-dopaminergic PPI models in identifying treatments for gating disturbances independently of their relevance to schizophrenia, bipolar mania, panic disorder, or other psychiatric disorders. Perhaps the most promising of such models is that based on PPI disruptions induced by acute NMDA antagonists. As discussed above, the PPI-disruptive effects of NMDA antagonists in rats and mice are clearly insensitive to most first-generation antipsychotic treatments but are attenuated by clozapine and some other second-generation anti-psychotics. Hence, the rodent model based on the disruption of PPI produced by NMDA antagonists may reveal information that is specifically relevant to the responsiveness of some neuroleptic-resistant patients to second-generation antipsychotics such as clozapine.

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