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Animal Models of Deficient Sensorimotor Gating in Schizophrenia: Are They Still Relevant?

Neal R. Swerdlow and Gregory A. Light

Abstract Animal models of impaired sensorimotor gating, as assessed by prepulse inhibition (PPI) of startle, have demonstrated clear validity at face, predictive, and construct levels for schizophrenia (SZ) therapeutics, neurophysiological endophenotypes, and potential causative insults for this group of disorders. However, with the growing recognition of the heterogeneity of the schizophrenias, and the less sanguine view of the clinical value of antipsychotic (AP) medications, our field must look beyond "validity," to assess the actual utility of these models. At a substantial cost in terms of research support and intellectual capital, what has come from these models, that we can say has actually helped schizophrenia patients? Such introspection is timely, as we are reassessing not only our view of the genetic and pathophysiological diversity of these disorders, but also the predominant strategies for SZ therapeutics; indeed, our field is gaining awareness that we must move away from a "find what's broke and fix it" approach, toward identifying spared neural and cognitive function in SZ patients, and matching these residual neural assets with learning-based therapies. Perhaps, construct-valid models that identify evidence of "spared function" in neural substrates might reveal opportunities for future therapeutics and allow us to study these substrates at a mechanistic level to maximize opportunities for neuroplasticity. Such an effort will require a retooling of our models, and more importantly, a re-evaluation of their utility. For animal models to remain relevant in the search for schizophrenia therapeutics, they will need to focus less on what is valid and focus more on what is useful.

Keywords Biomarker · Cognitive remediation · Mismatch negativity · Neurocognition · Prepulse inhibition · Schizophrenia

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1 Introduction

It is a fair assumption that for much of our history, and certainly since the emergence of our brain's capacity for introspection, humans have looked to infrahuman species for clues to understanding the complexities of our own thoughts, feelings, and behaviors. This "reverse anthropomorphism" reflects the compelling data from evolutionary biology that man's nervous system is fashioned on the neurobiological foundations of lower organisms (MacLean 1954; Karten 1991) as well as the perhaps less-compelling assumption that the infrahuman features retained in man's more advanced neural workings are informative about a brain that has acquired new and potentially emergent properties in abstract thought and complex emotions. It might be hard to pinpoint the first use of simple behaviors in infrahumans to understand human disorders. But studies of the late 1960s and early 1970s, from among others Michael Davis and his laboratory at Yale University (cf. Davis 1984), took one simple rodent behavior—the startle reflex—and developed a powerful laboratory-based assay for a simple cross-species behavior of relevance to human brain disorders. In this chapter, we review and critically evaluate the use of this simple behavior as part of a model with face, predictive, and construct validity for sensorimotor gating deficits in schizophrenia, and speculate on future applications of this model in the development of novel therapeutics for this disorder.

2 The Evolution of Prepulse Inhibition as a Validated Animal Model for Schizophrenia-Linked Neurobehavioral Deficits

The startle reflex is a constellation of responses to sudden, relatively intense stimuli. In humans, the blink reflex component of startle is measured using electromyography of orbicularis oculi; in laboratory animals, whole-body startle is quantified by

assessing the downward force resulting from the contraction of the skeletal muscles. Prepulse inhibition (PPI) occurs when a weak prestimulus 30–500 ms prior to the startling stimulus inhibits the startle response; this inhibition is an operational measure of sensorimotor gating (Graham 1975). While the inhibitory effect of the prepulse on the startle reflex is exerted in the pons, studies have described the limbic forebrain circuitry and descending pontine projections that regulate the inhibitory "tone" within the pons and determine the degree to which the prepulse inhibits the subsequent motor response (cf. Swerdlow et al. 1992a, 2001a, 2008). PPI thus appears to reflect the activation of "hardwired," centrally mediated inhibitory processes that are regulated by forebrain neural circuitry.

PPI is a useful experimental measure for understanding brain mechanisms for a number of reasons (Davis 1984). It is tested in an automated apparatus, under tight stimulus control, and stimulus parameters can be easily modified by the experimenter to elicit optimal response characteristics for studying a number of different aspects of this measure. Because PPI is a form of startle plasticity, it is measured using a "fight-or-flight" behavior that is simple, robust, and exhibited across all mammalian species tested to date. Of relevance to the present discussion, PPI is easily studied across species and has been investigated in mice (Carter et al. 1999; Francis et al. 2003; Frankland et al. 2004), rats (Swerdlow et al. 2001a), guinea pigs (Vaillancourt and Boksa 2000), pigs (Lind et al. 2004), and infrahuman primates (Linn et al. 2003), using stimulus parameters and equipment for stimulus delivery and response acquisition that are similar or identical to what are used in humans. This cross-species similarity in the appearance of the behavior and its response to parametric manipulations is the basis for the *face validity* of animal models that use PPI. While there appear to be differences in the neurochemical regulation of PPI across species (cf. Swerdlow et al. 2008), the basic parametric properties of PPI exhibit striking similarities from rodents to humans (e.g., Swerdlow et al. 1994a, b). Furthermore, PPI is under significant genetic control in both rodents (Francis et al. 2003) and humans (Greenwood et al. 2007).

Despite its advantages as a laboratory measure of simple brain processes, PPI would likely be a scientific footnote were it not for the fact that it is reduced in humans afflicted with any one of several different brain disorders. Compared with matched controls, PPI is deficient in patients with schizophrenia (e.g., Braff et al. 1978; Swerdlow et al. 2006), Huntington's disease (Swerdlow et al. 1995; Valls-Sole et al. 2004), obsessive-compulsive disorder (OCD) (Swerdlow et al. 1993; Hoenig et al. 2005; Ahmari et al. 2012), nocturnal enuresis (Ornitz et al. 1992), Asperger's syndrome (McAlonan et al. 2002), 22q11 syndrome (Sobin et al. 2005), Kleinfelter syndrome (Van Rijn et al. 2011), fragile X syndrome (Frankland et al. 2004), blepharospasm (Gomez-Wong et al. 1998), and Tourette syndrome (Castellanos et al. 1996; Swerdlow et al. 2001b).

Development and applications of PPI in animal models: While it is clear that PPI deficits are not clinically specific, the real catalyst behind the intense investigation of PPI came from the initial reports of PPI deficits in schizophrenia patients (Braff et al. 1978). With this 1978 study and its subsequent replication in almost 40 reports in the literature (cf. Swerdlow et al. 2014), investigators have viewed the

cross-species similarities in startle and PPI as an opportunity to leverage animal model studies to explicate the biology of this disorder. In the first connection of this initial report of PPI deficits in schizophrenia (Braff et al. 1978) with findings in experimental animals, evidence that startle inhibition by pulsating tactile tail pressure was eliminated after ablation of the nucleus accumbens (NAC; Sorenson and Swerdlow 1982) was viewed as potential evidence that accumbens dysfunction might contribute to the loss of startle inhibition by acoustic prepulses in schizophrenia; this suggestion has been substantiated by the number of subsequent reports, and 30+ years later, the NAC remains a central structure in current models for the regulation and dysregulation of PPI (e.g., Ma and Leung 2014).

A focus on the PPI-regulatory role of NAC dopaminergic systems (Swerdlow et al. 1986) and dopamine activity more broadly (Mansbach et al. 1988) was initially motivated by the prevailing hypothesis of a causative role of DA hyperfunction in the etiology of schizophrenia. The finding that PPI was disrupted in rodents by DA agonists (Swerdlow et al. 1986; Mansbach et al. 1988) was applied in a manner prescribed for animal models of that era, i.e., by assessing the ability of this pharmacological effect to predict the antipsychotic (AP) potential and potency of established and novel compounds (cf. Swerdlow et al. 1991, 1994b; Swerdlow and Geyer 1993). This approach differed from preexisting predictive models, such as apomorphine-induced canine emesis (Janssen and Niemegeers 1959), primarily because the behavior being measured (PPI) as a predictive index was analogous, if not homologous, across species. Thus, known AP compounds prevented the PPI-disruptive effects of DA agonists, and their potency in this assay correlated highly ($R = 0.99$) with their clinical AP potency (Swerdlow et al. 1994a, b). This compelling relationship is the basis for the *predictive validity* of this PPI model and led to the identification or validation of compounds with novel AP properties [e.g., ICI 204, 636 (quetiapine; Swerdlow et al. 1994a, b)].

The predictive model was expanded significantly by the observation that putative APs with novel chemical properties were distinguished by their ability to block the PPI-disruptive effects of NMDA antagonists (Johansson et al. 1994; Bakshi et al. 1994). Indeed, the prevailing wisdom of the early 1990s was that the ability to prevent the PPI-disruptive effects of NMDA antagonists such as phencyclidine and ketamine might predict the properties unique to "atypical" or second-generation APs (SGAPs) and thereby identify agents that would be both more clinically effective and better tolerated than first-generation APs. Over time, this approach ran into some experimental and clinical headwind. First, the ability to prevent NMDA antagonist-induced PPI deficits was not always specific to SGAPs [e.g., chlorpromazine blocks the PPI-disruptive effects of ketamine (Swerdlow et al. 1998)] or particularly sensitive to SGAPs (e.g., several studies reported either marginal or no ability of clozapine to prevent the PPI-disruptive effects of phencyclidine in rats). Second, and more importantly, clinical experience revealed that the benefits of SGAPs over older, first-generation APs were not robust, and in fact SGAPs carried a new and non-trivial list of adverse properties. Thus, while the predictive validity of these PPI models for antipsychotics were further extended in many informative ways as reviewed previously (e.g., Geyer et al. 2001; Swerdlow et al. 2008), they

ultimately must be seen in the more humbling context of the clinical reality that APs of any generation are not well-tolerated and have limited ability to enhance the function and improve the quality of life in schizophrenia patients (Lieberman et al. 2005). This is not to say that APs lack clinical value: In fact, APs appear to have utility in blunting the severity of acute psychotic symptoms, and their use is associated with a lower risk of adverse consequences of schizophrenia—from hospitalization to suicide (Palmer et al. 1999; Meltzer et al. 2003; Sun et al. 2007). Nonetheless, 20 years of experimentation with PPI as a model predicting AP efficacy and potency has done little to advance us toward treatments that achieve either greater clinical improvement or fewer significant adverse effects than those that predated this model.

One obvious advantage of animal models of a human behavior is that they make it feasible to study neural substrates and extrapolate from these substrates to corresponding circuitry in humans. Indeed, extending from the initial findings of a nucleus accumbens locus of forebrain PPI regulation (Sorenson and Swerdlow 1982; Swerdlow et al. 1986; Kodsi and Swerdlow 1994), this approach was applied to understand the neural basis of PPI deficits in schizophrenia and revealed that the forebrain substrates regulating PPI overlap somewhat with those implicated in the pathophysiology of this disorder. Thus, disturbances in prefrontal cortex (PFC), basal forebrain dopamine (DA) function, and thalamic and mesial temporal lobe function figure prominently in current models of schizophrenia neuropathology; similarly, PPI is potently reduced by experimentally induced manipulations of the medial PFC, ventral striatum, pallidum, thalamus, and mesial temporal lobe (cf. Swerdlow et al. 1992a, b, 2001a, 2008; Rohleder et al. 2014). The apparent overlap in the neural substrates regulating PPI, with those implicated in the pathophysiology of schizophrenia, is part of the support for the *construct validity* of animal models for impaired PPI in schizophrenia and has been used in an iterative cross-species strategy. In this strategy, PPI changes after neural circuit manipulations in laboratory animals have been used to develop and then test hypotheses about specific circuit disturbances in patients (e.g., Kumari et al. 2003), and in some cases, circuit-based therapeutics are being modeled based on PPI deficits in rats (e.g., Posch et al. 2012; Angelov et al. 2014; Ma and Leung 2014). Often, when substrates have been demonstrated to regulate PPI in rodents, the fact that PPI is deficient in schizophrenia patients has been used as the basis for justifying a fine grain analysis of those substrates in rats, in terms of their anatomical, neurochemical, and molecular properties. In turn, information about the detailed characteristics of this circuitry derived from studies in rodents has been used to support, develop, or test hypotheses regarding the nature of neural circuit disturbances in schizophrenia (e.g., Hines et al. 2013; Miller et al. 2010).

The construct validity of PPI models in rodents for PPI deficits in schizophrenia is also strengthened by the fact that experimental manipulations in rodents that are thought to model some of the suspected pathogenic insults contributing to schizophrenia also produce adult rodents with deficient PPI. Of the more studied models of this kind—social isolation rearing and neonatal ventral hippocampal

lesions—the former model was the subject of a recent review (Powell and Swerdlow 2015), and we will briefly review the latter model here.

In schizophrenia patients, the integrity of the hippocampal-PFC connection is reduced, and this deficiency predicts both neurocognitive and functional impairment (Hanlon et al. 2012). Lesions of the ventral hippocampus in neonatal rats (NVHLs) have been shown to recreate a number of deficits associated with schizophrenia (Lipska et al. 1993; Marquis et al. 2006; Angst et al. 2007; Marquis et al. 2008; cf. O'Donnell 2012), including reductions in PPI (Lipska et al. 1995; Le Pen and Moreau 2002; Le Pen et al. 2003; Daenen et al. 2003; Swerdlow et al. 2012a, b). To the degree that some forms of schizophrenia are characterized by aberrant ventral hippocampal development and connectivity, the NVHL model has been used to identify the expected "neuromaladaptive" consequences of such pathology and thereby help focus studies of pathophysiology and even therapeutics in this disorder. The model has been extended to demonstrate that a variety of early developmental insults to the mesial temporal lobe are accompanied by PPI deficits that emerge in adulthood, including immune/inflammatory activation of the VH (e.g., Zhu et al. 2014a, b; Ribeiro et al. 2013), neonatal pilocarpine-induced seizures (Labbate et al. 2014), and neonatal lesions of the basolateral amygdala (Vázquez-Roque et al. 2012). Other in utero or neonatal neurotoxic manipulations also produce PPI deficits in adult rats, including methylazoxymethanol (MAM) exposure (Le Pen et al. 2006), elevated neonatal allopregnanolone (Darbra et al. 2014), and neonatal administration of NMDA antagonists (Uehara et al. 2010). In some cases, the expression of PPI deficits induced by these early developmental manipulations can be blocked by acute treatments during adulthood, using antipsychotics (e.g., clozapine: Ribeiro et al. 2013), putative neuroprotective agents (e.g., minocycline: Zhu et al. 2014b), and glycinergic agents (Le Pen et al. 2003). Thus, it appears that PPI deficits are a common adult behavioral response to a wide range of perturbations in early rodent brain development, and particularly those that impact the mesial temporal lobe by various mechanisms. In total, this literature is consistent with the empirical evidence that PPI deficits are detected in many clinically and etiologically distinct brain disorders, as well as the prevailing wisdom that schizophrenia (and by extension its accompanying PPI deficits) reflects a heterogeneous neuropathology induced by any one or combination of a number of different possible early developmental insults.

Presumably, the failure to develop normal levels of PPI in these variations of the NVHL model could reflect many different underlying mechanisms. One potential mechanism implicated in recent studies is a developmental "hypercoupling" of forebrain regions (Chambers et al. 2010; Swerdlow et al. 2013a, b)—including PFC and nucleus accumbens (NAC)—due to the loss of their normal innervation by the ventral hippocampus (VH) after experimentally induced VH damage. Thus, the VH innervates both the PFC and the NAC, and conditions fostering greater PFC-NAC interconnectivity might be created by NVHLs via reduced competition at a synaptic level, or by the loss of a differentiating signal normally provided by VH innervation of either structure. NVHLs result in restructuring and electrophysiological changes within the PFC (Ryan et al. 2013), and hyper-correlated expression of

schizophrenia-linked genes in the PFC and NAC (Swerdlow et al. 2013a, b). Others have reported aberrant limbic–cortical connectivity associated with both endogenous (Anticevic et al. 2013) and drug-induced psychosis (Driesen et al. 2013) in humans; similarly, excessive fronto-striatal metabolic correlation ["Brain Lock" (Schwartz 1997)] has been demonstrated in other disorders associated with the reduced PPI, such as OCD. Importantly, in OCD, therapeutic response to medication or psychotherapy is associated with a metabolic "uncoupling" of fronto-striatal regions (Schwartz et al. 1996; Schwartz 1998). Perhaps, the most speculative but exciting concept to emerge from the NVHL/"hypercoupling model" is the possibility that an "uncoupling" of fronto-striatal circuitry might provide an avenue for early therapeutic interventions in schizophrenia. That such an "uncoupling" can be produced in OCD via cognitive interventions (Schwartz et al. 1996) may suggest such a therapeutic option in schizophrenia, as discussed below.

One approach to capitalize on the validity of PPI models has been to explore the genetic underpinnings of impaired PPI in rodents, to generate or support hypotheses related to the genetic basis of impaired PPI in schizophrenia [and other disorders (e.g., Castellan Baldan et al. 2014; Charles et al. 2014; Renoux et al. 2014)]. Given the numerous brain regions and interconnections known to regulate PPI, it is not surprising that these studies have identified a long list of genes that, by their deletion, suppression, or differential expression, lead to a modification in PPI or its sensitivity to pharmacologic disruption (cf. Swerdlow et al. 2008). A number of creative strategies have been used to understand this complex genetic landscape and its overlap with brain circuitry, via assessing the PPI-altering effects of gene knockouts, humanized gene insertions (e.g., Risbrough et al. 2014), strain differences in regional gene expression (e.g., Shilling et al. 2008), drug-induced changes in regional expression of genes identified in postmortem schizophrenia brain tissue (e.g., Dietz et al. 2014), and pharmacogenetic manipulations of neural activity in targeted neuron populations via the use of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) (e.g., Nguyen et al. 2014), among other techniques. These strategies are not without potential pitfalls, including the importance of assessing hearing loss in mutant animals as a potential basis for reduced inhibitory effects of auditory prepulses. More generally, the long list of candidate genes for which modification reduces PPI in rodents suggests limitations to the utility of this approach in clarifying the genetic basis of reduced PPI in schizophrenia. The use of genetic manipulations to understand the role of regionally selective cell populations and proteins in the regulation of PPI, however, continues to be a promising and informative experimental strategy.

But, just as the sobering news about the limited clinical value of APs limit the utility of PPI as a predictive model, there is sobering news about the heterogeneity of the neural and genetic substrates of schizophrenia that may limit the utility of PPI as a construct model. As noted below, published reports now catalog over twenty different brain regions with identifiable abnormalities in different cohorts of schizophrenia patients (cf. Levitt et al. 2010). Furthermore, current estimates suggest that over 100 loci explain 7 % of the risk for the development of schizophrenia (e.g., Schizophrenia Working Group of the Psychiatric Genomics Consortium

2014; Stefansson et al. 2014), and it is likely that only after we identify gene × gene and gene × environment interactions among these many risk variants will we ever account for a significant amount of the variance in the expression of the schizophrenia phenotype. Thus, though there is substantial basic scientific value in understanding brain circuits and candidate gene effects on behavior, it is not clear that the construct validity of PPI will bring us substantially closer to an understanding of the complex and heterogeneous neural and genetic bases for schizophrenia.

Of course, the neural and genetic heterogeneity of schizophrenia reflects, at least in part, the fact that this diagnosis is defined by clinical criteria that do not map neatly onto any single biological substrate. Perhaps, it does not make sense to judge the ultimate utility of a biological model, like PPI, based on its ability to clarify the treatments or neural basis for such an imprecise, non-biologically defined clinical entity. One could even argue that sensorimotor gating is a meaningful domain of brain function and that by identifying the neural substrates of PPI and its deficiency in subgroups of patients, we will establish a basis for categorizing brain disorders that is ultimately more valid and useful than the clinical nosology by which schizophrenia has been characterized to date. Clarity on whether such a use of PPI is feasible, or sensible, will need to await the substantial continued evolution of this model.

3 Where Are We Now?

Three decades after the first use of PPI in cross-species models for impaired sensorimotor gating in schizophrenia, we have substantial evidence supporting three levels of validity for these models. With these models, we have gained a reasonable understanding at a regional and circuit level of the neural regulation of PPI in rodents, and we have several pieces of evidence supporting the translation of this circuit "blueprint" onto the human brain and its regulation of PPI. Circuit models are being magnified within several brain regions—particularly the PFC, NAC, and VH—to explicate the regulation of PPI by these regions at the cellular and molecular level. This "circuit biology of PPI" is perhaps the most productive and still promising application of this cross-species model. But one great hope for PPI models, based on their strong predictive validity, has not yet materialized, as evidenced by the substantial limitations in the clinical impact of APs on neurocognition, function, and quality of life in schizophrenia populations. Indeed, it is in some ways the greatest failing of this animal model—that PPI studies in rodents do such an excellent job identifying compounds that reproduce the disappointing clinical impact of existing AP agents. One could argue that this failing is not unique to PPI models, and to some degree, it reflects a greater failing of modern psychopharmacology in its approach to therapeutics for complex polygenic disorders of neurodevelopmental origin with dispersed and heterogeneous neuropathology, like the schizophrenias. Perhaps, the most dispassionate assessment is that in our

extensive studies of PPI across species, we have developed models for which validity is clear, and yet utility is not.

4 What's Next: A Paradigm Shift in the Use of Cross-Species PPI Models for Enhancing Schizophrenia Therapeutics?

One unspoken assumption behind the anticipated utility of PPI as a model with predictive and construct validity is as follows: Because we can identify in rodents the neural circuitry regulating PPI and its deficiencies, we can determine ways to intervene within this circuitry to restore normal function, using PPI as a "readout." And, more importantly, we can then apply these restorative interventions, or derivatives thereof, to "fix what's broken" in the PPI-regulatory circuitry in schizophrenia patients and thereby impart therapeutic change. The failings in this "fix what's broken" assumption are apparent, once we review our current understanding of this disorder.

As it is currently conceptualized, the root cause of schizophrenia is an in utero and childhood developmental interruption and tangling of neural connections (Weinberger 1987; Murray et al. 1991; Lewis and Levitt 2002) that are orders of magnitude too complex to restore or replace. Failures of cell migration and axonal guidance begin early, and this compounds the unpredictability of forebrain disorganization, like a mechanical delay in the first of many tightly connecting trains. The absurdity of trying to "fix what's broken" is further appreciated by considering what happens when cells or fibers do not get to where they are supposed to be, at the time they are supposed to be there. When these passengers fail to arrive at their "final destinations," like the PFC, this triggers pre- and postsynaptic compensatory changes among many functionally distinct subregions and cell types, and convergent influences of neurotransmitters, peptides, and other neuromodulators, all within adjacent lamina. But it is not *just* the PFC: As noted above, the preponderance of findings in different schizophrenia cohorts support significant volumetric and/or morphometric abnormalities in over 20 brain regions (cf. Levitt et al. 2010). Calculate the permutations of synaptic interactions in the simplest cartoon schematic, the number of different risk genes, and the epigenetic events, and multiply by orders of magnitude, and one can easily appreciate the futility of expecting even the smartest drugs to "fix what's broken." The fundamental error in this "fix what's broken" approach to the development of pharmacotherapies for schizophrenia is that regardless of how valid the PPI animal model (or any other model, for that matter) may be, the drugs that it produces will not be able to reach backward two decades through a variable web of absent and misguided neural connections, and replace missing and improper ones with healthy ones. The sooner that we acknowledge that prefrontal and limbic-cortico-striato-pallido-thalamic dysfunction and dysmorphogenesis in schizophrenia are too widely distributed, complex, and variable to be "fixed" with medications and that the strategies for gene therapies would require interventions so

early in brain development as to present insurmountable ethical and logistical barriers for the foreseeable decades, the sooner we will be able to consider alternative strategies for applying animal models to the development of more successful therapeutics for this disorder. We do not presume to have found such a strategy, but we hope to begin the discussion about one approach that may warrant some attention.

4.1 Biomarkers to the rescue?

Biomarkers are objective measures that can be informative about a variety of different clinical characteristics, such as an individual's normal biology, their pathology including the trajectory of illness, or their response to a therapeutic intervention. They offer the hope that despite great heterogeneity and multivariate interactions in the pathogenesis of brain disorders, meaningful clusters of individuals can be associated with an objective measure and then reliably stratified in terms of the cause, course, and/or treatment sensitivity of a given disorder (Perez et al. 2014).

An assumption driving the search for psychiatric biomarkers is that the biology of these biomarkers will be simpler, more easily understood, and less heterogeneous than the biology of clinical psychiatric syndromes. But if the pathogenic pathways leading to schizophrenia are highly heterogeneous, we might expect that the biomarkers for these pathways might also be highly heterogeneous. Importantly, biomarkers might also be used to identify neural resources that *remain intact and functional in schizophrenia*. These functional "assets" might then be used to compensate for those lost to the aberrant developmental processes in this disorder. Such a model is applied successfully to stroke rehabilitation, where interventions are designed not to regrow brain circuitry that is lost or damaged, but rather to engage the normal physiological and anatomical properties of healthy brain circuits (e.g., in neighboring regions or parallel circuits) to restore or subsume the function of damaged ones (cf. Taub et al. 2002). In many forms of psychotherapy, the therapist's task is to identify an individual's psychological strengths (ego, intellectual, social, or otherwise) and then to engage them to overcome damaging thoughts or behaviors that are otherwise sustained by areas of psychological weakness. At a neural level, both stroke rehabilitation and psychotherapy engage viable and healthy systems to compensate for, or re-establish, functions lost to illness. Similarly, biomarkers of "health" that reveal a patient's neural "assets" can then be leveraged in the service of therapy.

In keeping with this model of using biomarkers to identify residual intact neural "assets," it is reasonable to consider whether *intact PPI* can be used as a biomarker of schizophrenia patients who might be capable of marshaling adequate neural resources to meet the demands of and reap the benefits of a particular therapeutic intervention. Consistent with such a model, Kumari et al. (2012) demonstrated that baseline PPI levels positively predicted the therapeutic response to cognitive–behavioral therapy (CBT) ($r = 0.69$ between pretreatment PPI (120 ms) and pre- versus post-CBT change in PANSS score). Schizophrenia patients who exhibited

the highest pre-therapy PPI levels were the ones who benefitted most from CBT, in terms of reductions in symptom severity. This finding supports the notion that higher PPI provides evidence of intact, functioning neural mechanisms, that positively predicts the therapeutic response to a cognitive intervention; it also harkens to the fronto-striatal "hypercoupling" state associated with PPI deficits in the NVHL model (above), since CBT has been demonstrated to metabolically "uncouple" fronto-striatal circuits in other clinical conditions (Schwartz et al. 1996).

Perhaps more importantly, this finding suggests that neural elements contributing to intact PPI in any given schizophrenia patients might enhance that individual's sensitivity to the therapeutic benefits of CBT. To the degree that intact sensorimotor gating reflects a generally "healthy brain," it is not surprising that patients with more intact brains would benefit more from learning-based therapies. *An unanswered question is whether a pharmacology for enhancing PPI in relatively intact nervous systems, applied to patients whose PPI is then enhanced by these agents, might be able to augment the therapeutic benefit of cognitive therapies in schizophrenia.* In other words, can a pharmacologically induced increase of sensorimotor gating serve as "readout" of a change in brain function that makes a patient more able to benefit from the therapeutic features of a cognitive therapy? This general paradigm called "PACT" (pharmacologic augmentation of cognitive therapies) has been utilized effectively in the treatment of anxiety disorders (e.g., Ressler et al. 2004) and is in the very early stages of development for application to schizophrenia patients, as described below.

4.2 Drug-Enhanced PPI as a Biomarker for PACT?

While many pharmacological agents are capable of disrupting PPI in intact rodents, relatively fewer are known to consistently enhance PPI. This may reflect the fact that, at baseline, mechanisms for sensorimotor gating function at their optimal levels; additionally, experimental stimulus parameters (in particular, prepulse intervals) are typically selected to maximize inhibitory effects of prepulses and thereby are most sensitive for detecting drug-induced reductions in inhibition. However, strains of both mice and rats have been identified with relatively low basal PPI levels, and investigators have also taken the strategy of identifying "low gating" rats within a particular strain, and in both cases, these strains and substrains have been shown to be more sensitive to PPI-enhancing effects of drugs or brain stimulation (Acheson et al. 2012; Angelov et al. 2014; Swerdlow et al. 2006). Roussos et al. (2008) reported parallel findings in humans, in which healthy subjects homozygous for the Val allele of the rs4680 COMT polymorphism exhibited low basal PPI levels and PPI-enhancing effects of the COMT inhibitor, tolcapone, while individuals homozygous for the MET allele of rs4680 exhibited high basal PPI and PPI-reducing effects of tolcapone. There are also rat strain differences in the sensitivity to PPI-enhancing versus disruptive effects of the same drugs, even among commonly used outbred rat strains (e.g., Swerdlow et al. 2004), that are independent of basal

PPI levels, and are associated with the differential expression of several genes, including COMT, within PPI-regulatory circuitry (Shilling et al. 2008).

Conceivably, by developing models sensitive to detecting the PPI-enhancing effects of drugs, we might identify candidates suitable for assessment in a PACT paradigm. A number of different drug classes have already been identified that enhance PPI, such as nicotinic agonists and certain SGAPs, but under specific experimental conditions, even psychostimulants can be shown to enhance PPI (cf. Swerdlow et al. 2008). Of course, these various drug effects might reflect sites of action anywhere from the PFC (Swerdlow et al. 2012a, b) to the pons (Pinnock et al. 2015) that might be more or less relevant to the ability of a drug to enhance the therapeutic impact of a cognitive therapy.

It is important to emphasize that, in the PACT model—unlike the traditional use of PPI as a predictive screen for AP efficacy—the ability of a drug to enhance PPI does not predict that giving that drug to an individual with schizophrenia will, by itself, have any therapeutic value. Indeed, our expectation would be that if a patient is treated with such a drug without the concomitant delivery of a cognitive therapy, this treatment will have little value. Cognitive therapies place demands on patients to develop compensatory strategies for learning and remembering information. In so doing, they specifically activate prefrontal regions subserving working memory and attention (Kumari et al. 2009; Haut et al. 2010). Patients will benefit most from cognitive therapies if they are able to meet the cognitive demands of these therapies, and drugs that facilitate this process—e.g., via the enhancement of sensorimotor gating, or activation of circuitries that lead to an enhancement of sensorimotor gating—should augment the benefits of cognitive therapies. Conversely, we would not predict that patients would benefit by taking these drugs and returning to an environment that lacks engagement with an active learning process.

We have begun to assess PPI-enhancing drug effects in rats as a predictor of utility in a PACT paradigm, using the low- to moderate-affinity NMDA-receptor antagonist, memantine. While NMDA antagonists are generally reported to disrupt PPI in rodents, PPI is actually increased in healthy subjects (HS) by NMDA antagonists such as ketamine (Duncan et al. 2001; Abel et al. 2003) and by the mixed NMDA antagonist/dopamine agonist, amantadine (Swerdlow et al. 2002). In intact rats, we detected PPI-enhancing effects of memantine, using relatively short (10–30 ms) prepulse intervals (Swerdlow et al. 2009). Based on this PPI enhancement, and reports of PPI-enhancing effects of ketamine and amantadine in healthy subjects (HS), we speculated that memantine would potentiate PPI in HS. Indeed, we reported that 20 mg memantine (po) enhanced PPI modestly across all HS (Swerdlow et al. 2009) and that this effect was most robust among HS with low basal PPI levels (Fig. 1a), and among HS scoring high on personality scales for novelty seeking, sensation seeking, and disinhibition. This set of findings provided us with a cross-species model in which PPI is enhanced by a drug within neurologically intact rodents and HS. Similar findings had been reported using the SGAPs, quetiapine (Swerdlow et al. 2006), and clozapine (Vollenweider et al. 2006).

Based on these findings in HS, we assessed the effects of memantine on PPI in schizophrenia patients (Chou et al. 2013a; Swerdlow et al. 2016). Our findings

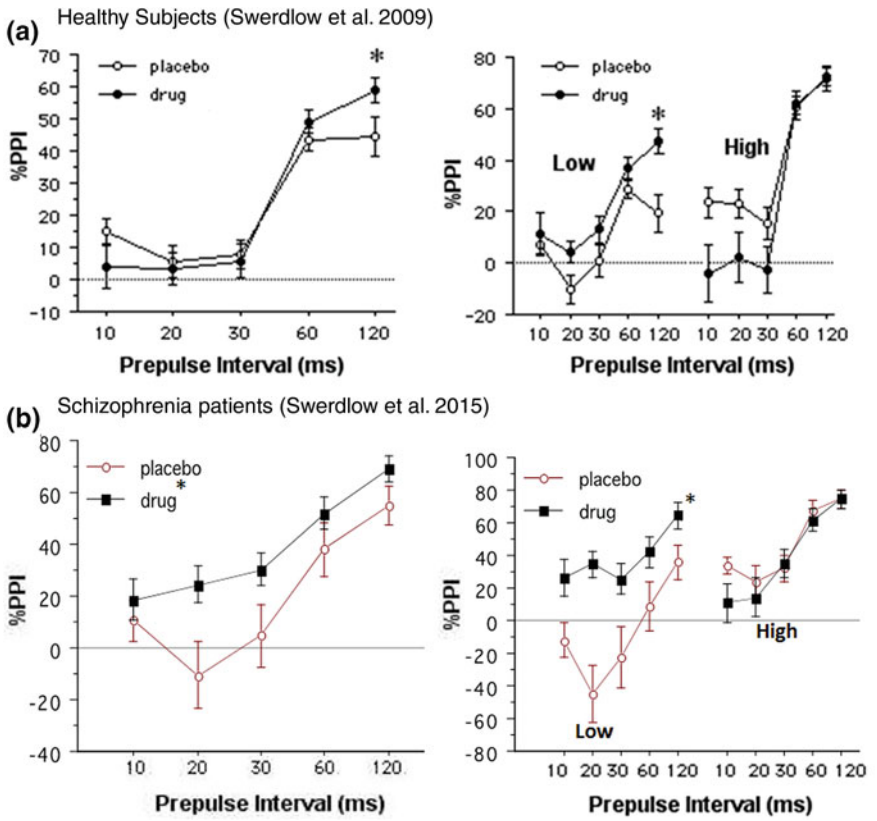

Fig. 1 **a** PPI in healthy subjects (HS) tested in a double-blind, placebo-controlled study of memantine (0 vs. 20 mg po), reported in Swerdlow et al. (2009). Data from all subjects are at *left*; at *right*, results are divided to show individuals with low versus high baseline PPI (grouped based on a median split). Memantine significantly enhanced PPI for 120-ms intervals in the inclusive group of HS (*asterisk*), but these effects were pronounced in "low gating" HS (*asterisk*) and absent in "high gating" HS. **b** Data from an identical paradigm in schizophrenia patients (Swerdlow et al. 2016). Again, memantine (20 mg po) significantly enhanced PPI in an inclusive group of schizophrenia patients (*left*; *asterisk*), and these effects were pronounced in "low gating" patients (*asterisk*) and absent in "high gating" patients. The next important question being assessed is whether PPI-enhancing effects of memantine predict properties beneficial to the therapeutic impact of a cognitive intervention in schizophrenia

suggest that schizophrenia patients are very sensitive to the PPI-enhancing effects of memantine (Fig. 1b), particularly among patients with low basal PPI levels; studies in progress are examining other potential predictors of memantine-enhanced PPI, as well as memantine-enhanced neurocognition in schizophrenia patients. These findings would suggest that the circuitry responsible for sensorimotor gating remains sufficiently intact and dynamic in schizophrenia patients to permit an increase in PPI in response to an acute drug challenge. Conceivably, this plasticity may represent a neural resource that could be engaged in a therapeutic capacity,

which is a core tenet of the "PACT" strategy (Swerdlow 2011a, b). This is not to say that a single dose of memantine would be expected to have therapeutic effects in schizophrenia patients; however, the neural signal elicited by this drug challenge provides evidence that mechanisms can be accessed that lead to neurobehavioral evidence of enhanced sensorimotor gating. Memantine engaged the "target" circuitry regulating PPI, and the resulting signal provides a metric of specific available neural resources within any given individual. The ultimate test of this "PACT" predictive model will be to determine whether memantine-enhanced PPI predicts sensitivity to the ability of memantine to augment the therapeutic benefits of a cognitive intervention in these patients. We are pursuing a similar design with other PPI-enhancing drugs from different chemical classes (Chou et al. 2013b; Swerdlow et al. 2013a, b; Bhakta et al. 2014).

5 Conclusion

Observations of deficient PPI in schizophrenia patients, and in patients with a number of other brain disorders, stimulated the development and extension of cross-species models deficient in PPI. Variations of these models have achieved face, predictive, and construct validity for the loss of PPI in schizophrenia patients. Predictive validity has confirmed AP potential in a number of established drugs and novel compounds, but has not yielded any "breakthrough" therapies for schizophrenia. Construct validity has been used to understand the neurobiology of developmental insults and genes that lead to deficient PPI in rodents, but there is no clear pathway from this new information to a deeper understanding of the anatomically and genetically heterogenous underpinnings of the schizophrenias. More generally, the fact that pathogenesis of the schizophrenias appears to begin very early in the brain development and is associated with variable abnormalities in perhaps dozens of brain regions makes it unclear how—despite their 3 levels of validity—PPI models will prove useful in identifying the causes of, or effective treatments for, these disorders. We have described our preliminary experience with an alternative use of cross-species measures of PPI, to identify plasticity within PPI-regulatory neural mechanisms, that might be leveraged toward augmenting the therapeutic impact of cognitive therapies. It is clearly too early to suggest an abandonment of other efforts to develop and apply other animal models of PPI, but at some point, it becomes worthwhile to move beyond models that are valid, in search of ones that might have clinical utility for our patients.

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