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REVIEW

Realistic expectations of prepulse inhibition in translational models for schizophrenia research

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Abstract
Introduction Under specific conditions, a weak lead stimulus, or "prepulse", can inhibit the startling effects of a subsequent intense abrupt stimulus. This startle-inhibiting effect of the prepulse, termed "prepulse inhibition" (PPI), is widely used in translational models to understand the biology of brain based inhibitory mechanisms and their deficiency in neuropsychiatric disorders. In 1981, four published reports with "prepulse inhibition" as an index term were listed on Medline; over the past 5 years, new published Medline reports with "prepulse inhibition" as an index term have appeared at a rate exceeding once every 2.7 days (n=678). Most of these reports focus on the use of PPI in translational models of impaired sensorimotor gating in schizophrenia. This rapid expansion and broad application of PPI as a tool for understanding schizophrenia has, at times, outpaced critical thinking and falsifiable hypotheses about the relative strengths vs. limitations of this measure.
Objectives This review enumerates the realistic expectations for PPI in translational models for schizophrenia research, and provides cautionary notes for the future applications of this important research tool.
Conclusion In humans, PPI is not "diagnostic"; levels of PPI do not predict clinical course, specific symptoms, or individual medication responses. In preclinical studies, PPI is valuable for evaluating models or model organisms relevant to schizophrenia, "mapping" neural substrates of deficient PPI in schizophrenia, and advancing the discovery and development of novel therapeutics. Across species, PPI is a reliable, robust quantitative phenotype that is useful for probing the neurobiology and genetics of gating deficits in schizophrenia.

Keywords Animal models · Antipsychotic · Dopamine · Prepulse inhibition · Schizophrenia · Sensorimotor gating · Startle

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Introduction

Among the paths to understanding the neurobiology of schizophrenia, one heavily traveled, has been the study through preclinical and clinical models of sensorimotor gating and its neural and genetic substrates. A laboratory paradigm frequently used to operationally measure sensorimotor gating is prepulse inhibition of the startle reflex (PPI). Medline lists over 1400 published reports utilizing the key word "prepulse inhibition" and over 580 that also include the key word "schizophrenia". Research using PPI to probe the neural and genetic bases of schizophrenia has crossed every level of the "top down" and "bottom up" investigations of this disorder—from studies of the psychological implications of PPI to those assessing the control of PPI by signal transduction pathways and the genes that regulate them. Arising implicitly and explicitly from such a broad application of the PPI paradigm have been assumptions and expectations that we hope to examine critically in this review. In so doing, we hope to offer some perspectives on both potentially productive directions of this work, and the degree to which some assumptions and expectations may, or may not, be reasonable.

Historical overview

The popularity of PPI as an experimental paradigm for understanding schizophrenia comes from its conceptual linkage to clinical observations that schizophrenia patients are unable to optimally filter or "gate" irrelevant, intrusive sensory stimuli (Bleuler 1911; Kraepelin and Robertson 1919; McGhie and Chapman 1961; Venables 1964). These clinical observations led to the formulation of a construct—"gating deficits" in schizophrenia—that has been extended to refer to deficient inhibition of both sensory and cognitive information. The PPI paradigm was developed as a measure of automatic or preconscious inhibition in normal comparison subjects, as one variant of numerous paired-pulse paradigms in which the presentation of a lead stimulus led to the reduced perceptual or motor response to a second stimulus (Peak 1939; Graham 1975) (Fig. 1). Braff et al. (1978) first merged the construct and its operational measurement by identifying PPI deficits in schizophrenia patients, a finding that has since been replicated by many independent groups and [as reviewed previously (Braff et al. 2001b) and below], has become among the most influential paradigms in the field of schizophrenia psychophysiology. A comprehensive review through the year 2000 of all reports linking PPI deficits to schizophrenia in clinical populations is found in Braff et al. (2001b); reports subsequent to this date are listed in Table 1. Animal studies first linked this finding to a neurochemical (DA) and anatomical (ventral striatum) substrate (Sorenson and Swerdlow 1982; Swerdlow et al. 1986), and subsequent reports centered these substrates within an extended forebrain and pontine circuit that regulates PPI in rodents (Koch and Schnitzler 1997; Swerdlow et al. 1992, 2000a; see Table 4). Animal studies have identified developmental (Geyer et al. 1993; Lipska et al. 1995; see Table 3) and genetic (Carter et al. 1999; Ralph et al. 1999; Geyer et al. 2002; see Table 3) influences on PPI and have led to predictive models for antipsychotic development (Swerdlow et al. 1994) that have been modified and widely applied towards antipsychotic discovery. A comprehensive review through the year 2000 of all reports using PPI in models predicting antipsychotic properties is found in Geyer et al. (2001); reports subsequent to this date are listed in Table 2.

This quantitative physiological abnormality in schizophrenia patients, conceptually linked to an intuitive clinical construct and neurochemical, anatomical, developmental, and genetic substrates, has provided a powerful focus for scientific developments. With the rapid expansion and broad application of variations of PPI measures, new expectations for its use to inform us about the biology of schizophrenia have at times outpaced critical thinking and falsifiable hypotheses about the relative strengths vs limitations of these complex studies. Here, we hope to enumerate some of these expectations and the future promises and potential limitations of PPI studies.

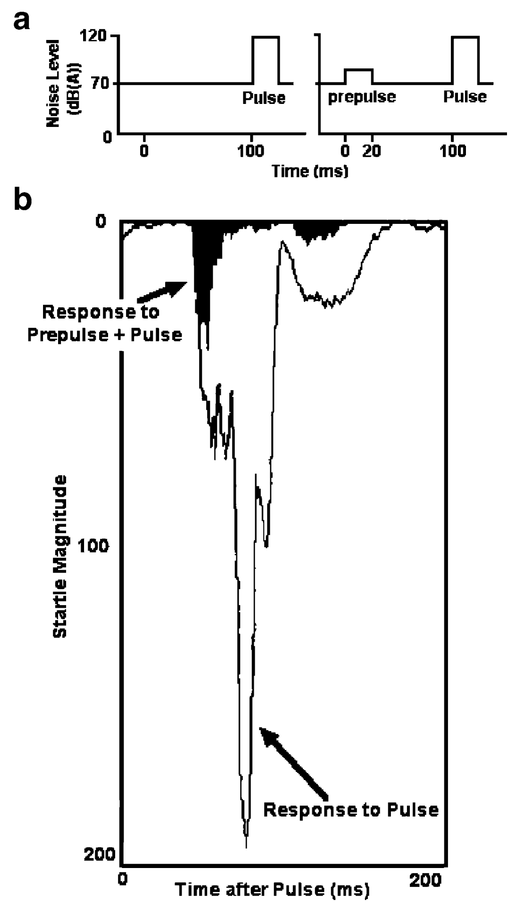

Fig. 1 Schematic representation, adapted from Swerdlow et al. (1994), of stimuli used to elicit PPI in laboratory measures (**a**). **b** shows superimposed tracings of electromyography of the right orbicularis oculi in an adult male subject, from sequential trials that included either a prepulse [20 ms noise burst 4 dB over a 70-dB(A) background] followed 100 ms later by a 118-dB(A) 40 ms startle noise pulse (*solid black area*), or the startle pulse alone (*open area*). Tracings in (**b**) begin at pulse onset. The amount of inhibition generated by the prepulse can be appreciated visually by subtracting the solid area from the open area

Human studies: What can our field realistically expect to learn about schizophrenia based on studies of PPI in humans?

Diagnosis

As an isolated measure, PPI is not a "diagnostic instrument". There is substantial variability and significant overlap in PPI distributions among normal and disordered populations. In addition, there are many different disorders

Table 1 Studies of PPI in schizophrenia patients and related groups, ca. 2001–2007[a]

I. Studies reporting PPI deficits in schizophrenia patients
II. Studies reporting PPI deficits in subgroups of schizophrenia patients
III. Studies reporting PPI deficits in schizophrenia patients under specific experimental conditions
IV. Studies reporting PPI deficits in schizophrenia patients
V. Studies reporting PPI deficits in populations conceptually linked to schizophrenia

Reference	Sex, medications, n, other characteristics	PPI deficits compared to normal comparison subjects (NCS)?	Other measures or factors examined in relation to PPI[b]	Eye side	Background DB[c]	Startle stimuli	Prepulse stimuli	Prepulse interval (ms)
I. Studies reporting PPI deficits in schizophrenia patients								
Braff et al. 2005	F, MED (n=25)	Yes		R	70	40 ms 115 dB WN	20 ms 78 and 86 dB WN	30, 120
Cadenhead et al. 2002	M/F 10/11, MED (n=4), UNMED (n=17)	33% of PTS<1 SD of PPI of NCS	Medication, clinical characteristics, P50, AS	R,L	70	40 ms 115 dB WN	20 ms 86 dB WN	30, 120
Duncan et al. 2003a	M, MED (n=27), UNMED (n=14)	Yes	Medication	R	70	40 ms 116 dB 1 KHz	20 ms 85 dB 1 KHz	30–120
Duncan et al. 2003b	M, study 1: pre- and post-medication (n=16); study 2: MED (n=43), UNMED (n=21)	Yes, independent of medication status	Medication	R	70	40 ms 116 dB 1 KHz	20 ms dB 1 KHz	30–120
Heresco-Levy et al. 2007	M/F 18/12, MED	Yes	Clinical characteristics, serum glycine and glutamate levels	R	70	40 ms 115 dB 1 KHz	20 ms 84 dB 1 KHz	30–120
Hong et al. 2007	M/F 46/13, MED	Yes	Medication, P50	R	70	40 ms 116 dB WN	20 ms 80 dB WN	30–500
Kumari et al. 2003a	M, MED (n=7).	Trend towards lower PPI	fMRI	R	None	40 ms airpuff 30 psi	20 ms airpuff 10 psi	100
Kumari et al. 2005a	M, MED (n=23)	Yes	Medication, violence ratings, clinical characteristics, illness duration	R	70	40 ms 115 dB WN	20 ms 85 dB WN	30–150
Kumari et al. 2005b	Study 1: M, MED (n=35–39); study 2: M/F 23/12, MED	Yes	Medication, clinical characteristics, AS	R	70	40 ms 115 dB WN	20 ms 85 dB WN	30–120
Kumari et al. 2007B	M/F 17/3, UNMED	Yes		R,L	70	40 ms 115 dB WN	20 ms 85 dB WN	30–120
Ludewig and Vollenweider 2002	M/F 49/18, MED	Yes	Medication, clinical characteristics	R	70	40 ms 115 dB WN	20 ms 86 dB WN	30–2000
Ludewig et al. 2002	M/F 15/4, MED	Yes		R	70	40 ms 115 dB	20 ms 86 dB	30–2000
Ludewig et al. 2003	M, UNMED (n=24)	Yes	Clinical characteristics	R	70	40 ms 115 dB WN	20 ms 86 dB WN	30–2000
Mackeprang et al. 2002	M/F 14/6, MED	Yes independent of medication status	Medication	R	70	40 ms 116 dB	85 dB	30–120
Perry et al. 2002	M and F (n=41); M/F 25/16, MED (n=20), UNMED (n=21)	Yes	Medication	R	70	40 ms 115 dB WN	20 ms 95 dB WN	30–120

Reference	Sex, medications, n, other characteristics	PPI deficits compared to normal comparison subjects (NCS)?	Other measures or factors examined in relation to PPI[b]	Eye side	Background DB[c]	Startle stimuli	Prepulse stimuli	Prepulse interval (ms)
Perry et al. 2004	M/F 8/6, MED	Yes	Sex	R	70	40 ms 115 dB WN	20 ms 85 dB WN	30–120
Swerdlow et al. 2006f	M/F 72/31, MED (n=94), UNMED (n=9)	Yes	Medication, sex, clinical characteristics, neurocognitive and functional measures, smoking	R,L	70	40 ms 115 dB WN	20 ms 85 dB WN	20–120
II. Studies reporting PPI deficits in subgroups of schizophrenia patients								
Kumari et al. 2004	M/F 27/15, MED	Yes in men, but not in women	Medication, sex, clinical characteristics, PPF	R	70	40 ms 115 dB WN	20 ms 78 or 85 dB WN	30–150
Leumann et al. 2002	M/F 25/8, MED	Yes with typical but not atypical APs	Medication, LI	R	70	40 ms 115 dB	20 ms 86 dB	30–2000
Meincke et al. 2004	M/F 22/14, MED	Yes during acute, but not remitted clinical state	Clinical characteristics, psychopathological symptoms	R	65	20 ms 115 dB WN	20 ms 73 dB WN	30, 100
Minassian et al. 2007	M/F 16/7, admission: MED (n=15), UNMED (n=8), 2 weeks later: MED (n=23), UNMED (n=1)	Yes at hospital admission, but not 2 weeks later	Medication, clinical characteristics	R	70	40 ms 115 dB WN	20 ms 85 dB WN	30–120
Oranje et al. 2002	M/F 31/13, MED	Yes in PTS with typical but not with atypical APs	Medication	R	NS	30 ms 115 dB 1 KHz	30 ms 80 dB 1.5 KHz	120
Quednow et al. 2006	M/F 19/9, pre-study: MED (n=9), UNMED (n=16), post-randomization: typical APs (n=12), atypical APs (n=16)	Yes during baseline session in first week of treatment, but not after prolonged treatment	Number of previous episodes, clinical characteristics, therapeutic success	R	70	40 ms 116 dB	20 ms 86 dB	120
III. Studies reporting PPI deficits in schizophrenia patients under specific experimental conditions								
George et al. 2006	M/F 9/6, smokers, MED	Smoking abstinence: ↓PPI; smoking reinstatement: ↑PPI	Smoking	NS	70	40 ms 115 dB WN	20 ms 85 dB WN	30–120
Hazlett et al. 2003	M/F 14/4, UNMED PTS with schizotypical personality disorder	Greater PPI during attended vs. ignored prepulses in NCS, but not in PTS	PPF	R	45	40 ms 104 dB WN	5 or 8 s 70 dB 0.8 or 1 KHz	120, 240
Kedzior and Martin-Iverson 2007	M/F 7/1, MED	deficits in “attend” condition only	Smoking	L[d]	60	50 ms 100 dB WN	20 ms 70 dB 5 KHz	20–200
Kumari et al. 2002	M, MED (n=30)	Yes in PTS treated with typical APs but not with RIS	Medication, clinical characteristics, duration of illness	R	70	40 ms 115 dB WN	20 ms 85 dB WN	30–120

Kumari et al. 2003b	M/F 7/4, MED (n=11)	↓ PPI in response to procyclidine		R	70	40 ms 115 dB WN	20 ms 78 or 85 dB WN	30–120
Wynn et al. 2004	PTS: M/F 74/2, MED (typical APs (n=22), atypical APs (n=43), mixed or unknown (n=11), unaffected siblings: M/F 17/19	No PPI deficits in PTS or unaffected siblings	Medication, PPF, sex, clinical characteristics	L	None	50 ms 105 dB WN	20 ms 75 dB WN	120
IV. Studies reporting no PPI deficits in schizophrenia patients								
Duncan et al. 2006a	M, MED (n=52), UNMED (n=21)	No	Medication, clinical characteristics	R	70	40 ms 116 dB 1 KHz	20 ms 85 dB 1 KHz	30–120
Postma et al. 2006	M, MED (n=9)	No. Smoking enhanced PPI in PTS and NCS	fMRI	R	None	40 ms airpuff 30 psi	20 ms air airpuff 10 psi	30–120
Volz et al. 2003	M/F 23/26, MED (n=42), UNMED (n=7)	No		L	NS	50 ms 100 dB WN	Pictures presented for 6 s	150–3,800
V. Studies reporting PPI deficits in populations conceptually linked to schizophrenia								
Kumari et al. 2005d	M/F 4/15, unaffected siblings of SZ PTS	Reduced PPI in siblings of SZ PTS with binaural stimulus presentation	Schizotypy ratings	R	70	40 ms 115 dB WN	20 ms 85 dB WN	30–120
Sobin et al. 2005a	M/F 11/14, children with 22q11 DS	Yes	Sex, age, clinical characteristics, latency reduction, attention network test, reaction time	R	50	50 ms 104 dB WN	40 ms 70 dB WN	100
Sobin et al. 2005b	M/F 13/12, children with 22q11 DS	Yes	Sex, age, clinical characteristics, symptom severity, subsyndromal symptoms of other disorders	R	56	50 ms 104 dB WN	30 ms 70 dB WN	100
Weike et al. 2001	Ss "believe in extraordinary phenomena" (n=16, M/F=5/11) or not (n=16, M/F=10/6)	PPI not different between believers and non-believers	Sex, age, schizotypal personality, magical ideation/perceptual aberration scales	L	NS	50 ms 105 dB WN	20 ms 1000 Hz	30–480

APs Antipsychotics, *AS* anti-saccade measures, *F* female, *fMRI* functional magnetic resonance imaging, *L* left, *LI* latent inhibition, *M* male, *MED* medicated, *NCS* normal comparison subjects, *NS* not specified, *P50* P50 event-related potential suppression, *PPF* prepulse facilitation, *PPI* prepulse inhibition, *PTS* patients, *R* right, *RIS* risperidone, *Ss* subjects, *SZ* schizophrenia, *UNMED* unmedicated, *WN* white noise, ↓ reduced, ↑ increased

[a] All tables are preceded by outlines describing their organizational structure. In distilling this substantial literature into tabular form, a substantial amount of information is lost. The abbreviated descriptions herein cannot do justice to the wealth of data and interpretations found in the original reports. References are provided to guide readers to the source material.

[b] Demographics reported as independent measures in most studies

[c] All dB A scale unless not specified in text; stimuli described in KHz are pure tones.

[d] Right eye, n=1

in which affected individuals are characterized by reduced PPI, on average, compared to a normal comparison population (cf. Braff et al. 2001b). The reason for the “non-pathognomonic” nature of PPI deficits is simple: the amount of PPI exhibited by any organism at any given moment reflects activity at many different levels of integrated cortico–striato–pallido–thalamic (CSPT) circuitry and its output via the pontine tegmentum. Low levels of PPI can result from normal variations at several levels of this circuitry; alternatively, disease processes can impact different levels of this circuit, with synergistic effects on pontine activity that mediates PPI. Conceivably, disease processes might even impact this circuitry in such a way as to bias it towards elevated levels of PPI, and compensatory or allostatic changes within feedback or downstream elements of the circuitry might offset the effects of otherwise PPI-disruptive disease processes. Thus, absolute levels of PPI—either low or high—are neither diagnostically nor neurophysiologically specific.

A corollary of this fact—that PPI is not “diagnostic”—is that no simple qualitative value of “normal” or “deficient” can accurately be applied to any particular level of PPI, particularly among clinically normal individuals. It is common in the literature (including our own reports) to describe relatively low levels of PPI as “deficient”, “impaired”, or “poor”. In fact, we know of no clear adaptive or functional advantage of higher vs. lower levels of PPI among clinically normal individuals. Perhaps, this idea is most easily conveyed in the comparison between clinically normal men and women: on average, under specific stimulus conditions (e.g., 20 ms white noise prepulses, 10 dB over a 70-dB(A) white nose background, 100 ms before a 115-dB(A) 40 white noise pulse), men exhibit more PPI than do women (Swerdlow et al. 1993b, 2006f; Kumari et al. 2004; Aasen et al. 2005). Furthermore, there is some evidence that among normal women, PPI shifts across the menstrual cycle (Swerdlow et al. 1997; Jovanovic et al. 2004). Clearly, there is no basis for describing PPI in women vs. men as “deficient”, nor for describing luteal- vs. follicular-phase PPI as “impaired”. Similarly, drugs that increase PPI in normals cannot be accurately claimed to “improve” PPI.

At a more basic level, at any given moment in time, individuals are not characterized by a single “PPI” value, in the same manner in which they might be characterized by other quantitative traits such as height, Q–T interval, or fasting glucose level. One of PPI’s strengths as an experimental measure is its exquisite sensitivity to stimulus parameters and test conditions [as described for the startle reflex by Davis 1984]. The inhibition generated by prepulses under different stimulus conditions likely reflects different underlying physiological substrates. Thus, under a variety of test/stimulus conditions, the same clinical population might conceivably exhibit PPI levels that are reduced, equal to, or elevated, compared to normal comparison subjects. An instructive example from preclinical studies of PPI is found in the report that inbred Brown Norway (BN) rats exhibit “deficient” PPI compared to outbred Sprague Dawley (SD) rats, based on measurements with 100 ms prepulse intervals (Palmer et al. 2000). Subsequent studies reproduced this finding, but also demonstrated that at shorter prepulse intervals, the opposite relationship existed: BN rats exhibited significantly *more* PPI compared to SD rats (Swerdlow et al. 2006a, 2008). Thus, depending on the stimulus parameters, populations can exhibit either relatively reduced or excessive PPI.

PPI is also highly sensitive to state variables and influences, such as medications (Table 1), cigarette smoking (Table 1), fatigue (van der Linden et al. 2006), stress (Grillon et al. 1998), and hormonal status (Swerdlow et al. 1997; Jovanovic et al. 2004). While some of these variables and influences can be controlled under experimental conditions, the notion of using such a sensitive measure in isolation as a diagnostic tool is not realistic. This being said, one potentially valuable strategy in the characterization of clinical populations is the use of PPI in combination with multiple other measures of forebrain inhibitory function, such as P50 event-related potential (ERP) suppression (“P50 gating”; Adler et al. 1982) and antisaccade deficits (Radant et al. 2007), to identify multiple measures and patterns of normal vs. deficient function (Cadenhead et al. 2002; Braff et al. 2008; Sugar et al. 2007). PPI and P50 gating are both deficient but correlate weakly, if at all, in schizophrenia patients (Braff et al. 2007b); similarly, PPI and antisaccade performance are both deficient but do not correlate significantly in schizophrenia patients (Kumari et al. 2005b). Thus, these measures apparently assess forebrain inhibitory processes that are dissociable and nonredundant. More importantly, there are patients who exhibit normal levels of some but not other gating measures (and presumably normal function within brain circuitry regulating some but not other measures), and subpopulations of patients who exhibit different profiles in these deficits (Kumari et al. 2005b; Swerdlow et al. 2006f; Braff et al. 2007b). These subpopulations may reflect different patterns of brain dysfunction and conceivably distinct genetic substrates and treatment sensitivities (Braff et al. 2007a).

Symptoms, course, and outcome

Can we predict the clinical course or even clinical features of schizophrenia based on PPI levels? There is no compelling data to suggest that among schizophrenia patients, levels of PPI predict clinical course, nor are there consistent robust relationships between lower levels of PPI and higher levels of specific symptoms of schizophrenia, or cumulative

Table 2 Examples of studies using PPI to assess or predict antipsychotic properties, ca. 2001–2007

I. Anti-dopaminergics	VII. Cannabinoid mechanism
A. D2/mixed receptor antagonists	A. CB1-antagonists
B. D3-preferential antagonists	B. Endocannabinoid transport inhibitor
C. D4-preferential antagonists	C. Cannabidiol
II. Glutamatergic mechanisms	VII. Neuropeptide mechanisms
A. mGLUR	A. Neurotensin agonists
B. NMDA	B. Opioids
C. GLY	C. CCK
III. Serotonergic mechanisms	IX. Adenosine mechanisms
IV. Noradrenergic mechanisms	X. GABA agonists
V. Cholinergic mechanisms	XI. GABA agonists
A. Nicotinic agonists	XII. Hormones
B. Muscarinic agonists	XIII. Second-messenger inhibitors
C. AChE inhibitors	A. Nitric oxide synthase inhibitors
VI. Histaminergic mechanisms	B. Guanylate cyclase+NOS inhibitors
	C. PDE-inhibitors
	XIV. Miscellaneous

References	Species, strain, sex	PPI deficit induced by	Primarydrug/mechanismtested	Effects	Other drug types tested
I. Anti-dopaminergics					
A. D2/mixed receptor antagonists					
	Rats				
Bast et al. 2001	WI, M	Intra-VHPC NMDA infusion	**HAL** D_2 family antagonist	∅NMDA	CLO (∅NMDA)
Cilia et al. 2007	SD, M	KET	**HAL**	∅KET, not potentiated by mGLUR5 antagonist MPEP	CLO, RIS, lamotrigine, SB-271046-A (all similar effects to HAL)
Conti et al. 2005	WKY, M; BN, M	ICV CRF infusion	**HAL**	↓CRF in WKY rats, ∅CRF in BN rats	CLO (↓CRF in WKY rats, overcompensation of PPI-deficit in BN rats)
van den Buuse and Gogos 2007	SD, M	8 OHDPAT	**HAL**	↓8 OHDPAT (at 100 ms PP interval)	RAC, ARI, BUS (all ↓8-OHDPAT), CLO, OLA, RIS, AMI, MDL73,005EF (partial 5-HT_{1A} agonist) (all ∅8-OHDPAT) all at 100 ms PP interval
	Rats + mice				
Metzger et al. 2007	Mice, C57; Rats, SD, M	AMP or APO	**HAL** (implanted HAL polymer, or acute HAL)	HAL implants: ↓AMP in mice, ↓APO in rats Acute HAL: ↓APO in rats	
	Mice				
Russig et al. 2004	C57, M	APO	**HAL**	↓APO	CLO (∅APO)

Table 2 (continued)

References	Species, strain, sex	PPI deficit induced by	Primarydrug/mechanismtested	Effects	Other drug types tested
	Human subgroups (+rats)				
Vollenweider et al. 2006	Humans ("low vs. high gaters")	Basal PPI, differences between subgroups	**CLO** D_{1-4}/5-HT_2/α_1/ muscarinic antagonist	↑PPI in "low gaters" (at short PP intervals), ∅PPI in "high gaters"	
Swerdlow et al. 2006a	Humans ("low vs. high gaters"), M; rats, SD, M; rats, BN, M	Basal PPI, differences between human subgroups or rat strains	**Quetiapine** D_{1-2}/5-HT_2/α_1/H_1/ muscarinic antagonist	↑PPI in human low gaters and SD rats (at short PP intervals), ↑PPI in BN rats	CLO (↑PPI at short PP intervals), HAL (∅PPI) in SD rats
	Primates				
Linn et al. 2003	Capuchin monkeys, F	PCP	**CLO**	↓PCP	HAL (∅PCP)
	Rats				
Erhardt et al. 2004	SD, M	↑Endogenous KYNA by kynurine or PNU 156561A	**CLO**	↓KYNA	HAL (↓KYNA)
Le Pen and Moreau 2002	SD, M	nHPC lesion	**CLO**	↑PPI	OLA (↑PPI), RIS (↑PPI), HAL (∅PPI)
Depoortere et al. 2007b	SD, M	APO	**F15063** D_2/D_3-Antagonist, D_4-partial agonist, 5-HT_{1A}-agonist	↓APO	
Depoortere et al. 2007a	SD, M	Basal PPI	**F15063**	∅PPI	
Barr et al. 2006	SD, M	IR vs. induction of PPI deficits by APO, PCP, or CIR in SR rats	**Iloperidone** DA/5-HAT/ NA antagonist	∅PPI in IR rats, but ↓APO, ↓PCP, ↓CIR in SR rats	
Ellenbroek et al. 2001	WI, M	Basal PPI, APO, or AMP	**JL13** Predominant D_1/5-HT_2 binding	↑PPI (basal), ↓APO, ↓AMP	HAL, CLO (both, ∅PPI (basal), ↓APO, ↓AMP)
Ojima et al. 2004	SD, M	Basal PPI	**Perospirone** D_2/5-HT_{2A}/ 5-HT_{1A} antagonist	↑PPI	HAL (∅PPI), RIS (↑PPI (relative to HAL))
Rueter et al. 2004	SD, M	nVHPC lesion	**Risperidone** D_2/5-HT_2/α antagonist (chronic low-dose treatment)	↑PPI	CLO (↑PPI)
Bubenikova et al. 2005	WI, M	DIZ	**Zotepine** D_1/D_2/ D_3/5-HT_{2A}/ 5-HT_{2C}5-HT_6/5-HT_7/α_1/H_1/ NET-affinity	∅DIZ	RIS (∅DIZ), CLO, OLA (both ↓DIZ, but ↓PPI relative to vehicle (no DIZ))
	Mice				
Fejgin et al. 2007	NMRI, M	Basal PPI or PCP	**Aripiprazole** partial agonist at D_2/5-HT_{1A} and antagonist at 5-HT_{2A}	↑PPI (basal), ↓PCP	CLO (↑PPI (trend), ∅PCP), OLA, (∅PPI, ∅PCP), HAL (↑PPI, ∅PCP)
Brea et al. 2006	Swiss, M	APO or DOI	**QF2004B** D_{1-4}/5-$HT_{1A,2A,2C}$/ $\alpha_{1,2}$/$M_{1,2}$/H_1-binding	↓APO, ↓DOI	CLO, HAL (both ↓APO, ↓DOI)
Flood et al. 2008	DBA/2NCrl, DBA/2J, 2NHsd, 2NTac1, 2NTac2, C57BL/6Tac, 129S6/SvEvTac	Basal PPI	**Olanzapine** D_1/D_2/5-HT_2/α_1/ muscarinic/H_1 antagonist	Reversal of PPI deficit (tested only in DBA/2NCrl mice)	ARI (reversal of PPI deficit), β-CD (reversal of PPI deficit compared to H_2O) in DBA/2NCrl mice; both drugs were not tested in other strains

B. D3-preferential antagonists					
	Rats				
Zhang et al. 2007b	WI, M	PD128907 (D3 agonist), or APO	**A-691990**	↓PD128907, ∅APO	HAL (∅PD128907, ↓APO), RAC (∅PD128907), CLO, RIS (both: ↓PD128907, ↓APO), SB 277011 (↓PD128907, ∅APO)
	Mice				
Zhang et al. 2006	DBA, M	Basal PPI or nVHPC lesion	**A-437203**	↑PPI in unlesioned animals, but ∅PPI after nVHPC lesion)	Intact mice: HAL (↑PPI), RIS (↑PPI), SB277011 (D3 antagonist, ↑PPI), AVE 5997 (D3 antagonist, ∅PPI); nVHPC lesion: HAL (↑PPI), AVE 5997 (∅PPI); BP897 (preferential D3/D2 antagonist, ↑PPI in lesioned and intact mice)
Park et al. 2005	ICR, M	APO	**KKHA 761**	↓APO	
C. D4-preferential antagonists					
Boeckler et al. 2004	**Rats**, WI, M		**FAUC 213**	↓APO	
II. Glutamatergic mechanisms					
A. mGLUR					
	Rats				
Kinney et al. 2005	SD, M	AMP	**CDPPB** Metabotropic GLU 5 allosteric potentiator	↓AMP	
	Mice				
Galici et al. 2005	C57, M	AMP or PCP	**LY487379** Metabotropic GLU 2 allosteric potentiator	↓AMP, ∅PCP	LY379268 (GLU 2/3 agonist; ∅AMP, ∅PCP)
B. NMDA					
	Rats				
Zajaczkowski et al. 2003	WI, M	DIZ	**CGP 40116** Competitive NMDA antagonist	↓DIZ	
C. GLY					
	Rats				
Le Pen et al. 2003	SD, M	nVHPC lesion	**Glycine**	↑PPI	ORG 24598 (GLYT1 inhibitor, ↑PPI)
	Mice				
Adage et al. 2007	C57, M	PCP	**AS057278** DAAO inhibitor; DAAO is the enzyme which oxidizes D- serine (→ see below)	↓PCP	CLO (↓PCP)
Depoortere et al. 2005	DBA, M	Basal PPI	**SSR5504734** GLYT antagonist	↑PPI	
Kinney et al. 2003	DBA, M	Basal PPI	**NFPS** GLYT1 antagonist	↑PPI	CLO (↑PPI)
Lipina et al. 2005	C57, M	Basal PPI or DIZ	**D-Serine** modulator of the GLY site of the NMDA receptor	↑PPI (basal PPI), ∅DIZ	L-Serine (∅PPI), ALX 5407 (GLYT1 inhibitor, ↓PPI, ↓DIZ), CLO (↑PPI, ↓DIZ)

Table 2 (continued)

References	Species, strain, sex	PPI deficit induced by	Primarydrug/mechanismtested	Effects	Other drug types tested
III. Serotonergic mechanisms					
			5-HT1		
	Rats				
Auclair et al. 2006	SD, M	APO	**SSR181507** 5-HT1A agonist, partial D2 agonist	∅APO ↓APO (when co-administered with WAY100635)	SLV313 (similar to SSR81507), sarizotan (∅APO), bifeprunox, HAL, ARI, RIS, OLA, QUE, ZIP (all ↓APO)
Auclair et al. 2007	SD, M	Basal PPI	**SSR181507**	↓PPI (reversed by WAY100,635)	Sarizotan, bifeprunox, 8-OHDPAT, (all ↓PPI), HAL, ARI, RIS, OLA, QUE, ZIP (all ∅PPI)
Krebs-Thomson et al. 2006		5-MeO-DMT (hallucinogen)	**Way100,635** 5-HT_{1A} antagonist	↓5 MeO-DMT	M100907 (5-HT_{2A} antagonist, ∅5-MeO-DMT), SER-082 (5-HT_{2C} antagonist ↓5-MeO-DMT)
	Mice				
Sakaue et al. 2003	ddY, M	IR, APO or DIZ	**MC-242** 5-HT_{1A} agonist	↑PPI (in IR mice, antagonized by Way100,635), ∅APO (in SR mice), ∅DIZ (in SR mice)	RIS (↑PPI in IR mice, ↓APO in SR mice)
			5-HT2		
	Rats				
Vanover et al. 2006	SD, M	DOI	**ACP-103** 5-HT_{2A} inverse agonist	↓DOI	
Siuciak et al. 2007	WI, M	APO	**CP-809,101** 5-HT_{2C} agonist	↓APO	HAL (↓APO)
Ouagazzal et al. 2001a, b	SD, M	LSD (hallucinogen)	**M100907**	↓LSD	SB 242084 (5-HT_{2C} antagonist), SDZ SER 082 (5-$HT_{2b/2C}$ antagonist), RO 04-6790 (5-HT_6 antagonist), HAL (all ∅LSD)
	Mice				
Barr et al. 2004	DAT-KO, M	Basal PPI	**M100907** 5-HT_{2A} antagonist	↑PPI	
Marquis et al. 2007	DBA/2N, M	Basal PPI, DIZ, or DOI	**WAY 163909** 5-HT_{2C} agonist	↑PPI, ↓DIZ, ↓DOI, ↑AMP	
			5-HT_6		
Pouzet et al. 2002a	**Rats**, WI, M	AMP or PCP	**SB-271046** 5-HT_6 antagonist	↓AMP, ∅PCP	CLO (↓AMP, ∅PCP)
			5-HT7		
	Rats (+ mice)				
Pouzet et al. 2002b	WI, M	AMP or PCP	**SB-258741** 5-HT_7 antagonist	∅AMP, ↓PCP	RIS (↓AMP, ↓PCP)
	Rats + mice				
Semenova et al. 2008	5-HT7KO, M; Mice, C57, M; Rats, SD, M	APO, AMP, or PCP	**SB-269970** 5-HT_7 antagonist	No SB-269970: ↓PCP in KO vs. WT mice; ↓APO and ↓AMP in both KO and WT. SB-269970: ∅PCP in C57 mice and SD rats	

IV. Noradrenergic mechanisms					
	Rats				
Ballmaier et al. 2001a	SD, M		Coapplication of **Idazoxan** α_2 antagonist) + **RAC** (D2/D3 antagonist)	↓APO, but no additional impact of idazoxan over RAC	
Sallinen et al. 2007	SD, M; WI, M	PCP	**JP-1302** α_{2C} antagonist	↓PCP in both strains	Atipamezole (α_2 antagonist, ∅PCP)
V. Cholinergic mechanisms					
A. Nicotinic agonists					
	Rats				
Cilia et al. 2005	LH, M	IR	**Compound A** α7-agonist	↑PPI	
Suemaru et al. 2004	WI, M	APO or PCP	**Nicotine**	∅PPI, ↓APO (eliminated by mecamylamine, but not hexamethonium), ∅PCP	Methyllycaconitine (α_7 antagonist), dihydro-beta-erthoidine ($\alpha_4\beta_2$ antagonist), both ∅PPI, HAL (↓APO, ∅PCP), CLO (↓PCP)
	Mice				
Andreasen et al. 2006	BALB, M; NMRI, M	PCP	**Nicotine**	↓PCP in BALB mice, ∅PCP in NMRI mice	CLO (similar pattern than nicotine), RIS (∅PCP in either strain)
Spielewoy and Markou 2004	DBA, C3H, C57BL or 129, all M	PCP	**Nicotine**	∅PPI in all strains, ↓PCP in DBA and C3H (trend), ∅PCP in C57 and 129 mice	
B. Muscarinic agonists					
	Rats				
Jones et al. 2005	SD, M	APO or SCO	**Xanomeline** M1/M4 muscarinic agonist	↓APO, ↓SCO	BuTAC (M2/4-preferring agonist, ↓APO), oxotremorine, RS86, pilocarpine, milameline,sabcomeline (all muscarinic agonists, all ↓APO), HAL (↓APO, ↓SCO), OLA (↓APO), SCH23390 (∅CLO)
Stanhope et al. 2001	SD, M	APO	**Xanomeline**	∅PPI, ↓APO	HAL (∅PPI, ↓APO), pilocarpine (↓PPI, ∅APO), MUS (↓PPI), SCO (↓PPI), methyoscopolamine (∅PPI)
C. AChE-inhibitors					
	Rats				
Hohnadel et al. 2007	WI, M	APO, DIZ, or SCO	**Donepezil**	↓APO, ∅DIZ, ↓SCO	Galantamine (↓APO, ↓DIZ, ↓SCO)
Ballmaier et al. 2002	SD, M	Immunolesioning of cholinergic neurons in nucleus basalis	**Rivastigmine**	↑PPI	
VI. Histaminergic mechanisms					
Roegge et al. 2007	**Rats**, SD, M	DIZ	**Pyrilamine** H1 antagonist	↓DIZ	
	Mice				
Fox et al. 2005	DBA, M	Basal PPI	**ABT-239** H3 receptor antagonist	↑PPI	RIS (↑PPI)

Table 2 (continued)

References	Species, strain, sex	PPI deficit induced by	Primarydrug/mechanismtested	Effects	Other drug types tested
Ligneau et al. 2007	Swiss, M	APO	**BF2.649** H3 receptor antagonist/inverse agonist	↓APO	
Browman et al. 2004	DBA, M; C57, M	Basal PPI[a,(b)]	**Thioperamide** H3 receptor antagonist/inverse agonist	↑PPI in DBA, ∅PPI in C57 mice	Ciproxifan (↑PPI in DBA and C57 (trend), RIS (↑PPI in both strains)
VII. Cannabinoid mechanisms					
A. CB1 antagonists					
	Rats				
Ballmaier et al. 2007	SD, M	PCP, DIZ, APO	**AM251**	↓PCP, ↓DIZ, ↓APO	Rimonabant (↓APO, ↓ DIZ, ↓PCP), CLO (↓PCP)
	Mice				
Malone et al. 2004	Swiss, M	APO	**SR 141716**	↓APO	
Nagai et al. 2006	ddY, M	Δ9-THC	**SR 141716**	↓THC	HAL (↓THC), RIS (↓THC)
B. Endocannabinoid transport inhibitor					
Bortolato et al. 2006	**Rats**, SD, M	Basal PPI	**AM404**	∅PPI	Win55,212 (∅PPI), APO (↓PPI), DIZ (↓PPI)
C. Cannabidiol					
Long et al. 2006	**Mice**, Swiss, M	DIZ	**Non-psychoactive constituent of the Cannabis sativa** plant, agonist of the TRP receptor VAN1, inhibitor of anandamide-uptake	↓DIZ, ∅DIZ (if pretreated with TRP agonist capsazepine)	CLO (↓DIZ)
VIII. Neuropeptide mechanisms					
A. Neurotensin agonists					
	Rats				
Shilling et al. 2004	SD, M	DOI or CIR	**NT69L**	↓DOI, ↓CIR	PD149163 (NT antagonist, ↓CIR)
Shilling et al. 2003	SD, M	AMP or DIZ	**NT69L**	↑PPI, ↓AMP, ↓DIZ	
B. Opioids					
Bortolato et al. 2005	**Rats**, SD, M	U50488 kappa-opioid agonist	**Nor-BNI** Kappa-opioid antagonist	↓U50488, but ∅APO, ∅DIZ	CLO (↓U50488), HAL (∅U50488)
Ukai and Okuda 2003	**Mice**, ddY, M	APO	**Endomorphin-1** Endogenous mu opioid agonist (ICV-infusion)	∅PPI, ↓APO (antagonized by the mu1 antagonist naloxonazine, but not by ICV-infusion of the mu antagonist β-funaltrexamine)	Naloxonazine (∅APO)
C. CCK					
Shilling and Feifel 2002	**Rats**, SD, M	AMP, DIZ or DOI	**SR146131** CCK_A antagonist	∅AMP, ↓DIZ, ↓DOI	

IX. Adenosine					
Wardas et al. 2003	**Rats**, WI, M	PCP	**CGS 21680** Adenosine A_2 agonist	↓PCP	
X. GABA agonists					
Bortolato et al. 2004	**Rats**, SD, M	PPI, APO or DIZ	**Baclofen**	∅PPI, ∅APO,↓DIZ, (prevented by SCH50911)	
Bortolato et al. 2007	Juvenile **mice**: DBA, M; C57, M	Basal PPI in DBA (and C57)	**Baclofen**	↑PPI (prevented by SCH50911) in DBA, ∅PPI in C57 mice	CLO (↑PPI in DBA, ∅PPI in C57), HAL (∅PPI in both strains)
XI. Anticonvulsants/mood stabilizers					
	Rats				
Frau et al. 2007	SD, M	Basal PPI, APO or DIZ	**Topiramate** $GABA_A$ agonist, voltage-gated Na-channel, AMPA/Kainate blocker	↑PPI, ↓APO, potentiation of HAL (↓APO) and CLO (↓APO) effects, ∅DIZ, attenuation of CLO (↓DIZ)	HAL (↓APO), CLO (↓APO, ↓DIZ)
	Mice				
Brody et al. 2003a, b	129, M; C57, M	AMP, KET	**Lamotrigine** Na-channel blocker	↓KET in 129 mice, ∅AMP in both strains, ↑PPI in KET and ctrl mice (C57)	
	Mice				
Ong et al. 2005	129, M; C57, M	AMP or KET	**Lithium**	∅PPI[1,2], ↓AMP[1,2], ∅KET[1]	Carbamazepine (∅PPI, ↓KET, ∅AMP), Phenytoin (↑↓PPI (dose-dependent), ∅KET, ∅AMP), valproate (∅PPI, ∅KET, ∅AMP); all in 129 mice
Umeda et al. 2006	ddY, M	APO or DIZ	**Valproate**	∅PPI, ↓APO, ∅DIZ	Lithium (∅PPI, ↓APO, DIZ), carbamazepine (∅PPI, ↓APO, ↑DIZ)
XII. Hormones					
	Rats				
Czyrak et al. 2003	WI, M	8-OHDPAT	**Corticosterone** hormone	↓8-OHDPAT (repeated CORT), ∅8-OHDPAT (acute CORT)	Way100,135 (↓8OHDPAT)
Gogos and Van den Buuse 2004	SD, F, OVX	8-OHDPAT	**Estrogen** (implant, 2 weeks) sex hormone	↓8-OHDPAT, ↓8-OHDPAT (in cotreatment with progesterone)	Progesterone (implant, ∅8-OHDPAT)
Myers et al. 2005	SD, M	PCP	**Secretin** peptide functional in gut and brain	↓PCP	
XIII. Second-messenger inhibitors					
A. Nitric oxide synthase inhibitors					
	Rats				
Salum et al. 2006	WI, M	AMP, APO, BRO, QUI	**L-NOARG** (two injections)	↓AMP, but ∅APO, ∅BRO, (↓QUI (trend))	SKF38393 (∅PPI-independent of pretreatment with L-NOARG)
	Mice				
Klamer et al. 2005b	**Mice** deficient of neuronal NOS vs.	PCP or DIZ	**L-NAME**	↓PCP	

Table 2 (continued)

References	Species, strain, sex	PPI deficit induced by	Primarydrug/mechanismtested	Effects	Other drug types tested
	B6129SF2 (ctrl), M				
Klamer et al. 2004b	NMRI, M	PCP	*N*-**propyl-arginine**	↓PCP	
B. Guanylate cyclase + nos inhibitors					
Klamer et al. 2004a	**Mice**, NMRI, M	PCP	**Methylene blue**	↓PCP	
C. PDE-inhibitors					
Kanes et al. 2007	**Mice**, C57, M	PPI or AMP	**Rolipram** Phosphodiesterase (PDE)4 inhibitor	↑PPI, ↓AMP	HAL (↑PPI)
XIV. Miscellaneous					
	Rats				
Wang et al. 2003a	SD,	Perinatal PCP (3 applications)	**M40403** Superoxide Dismustase Mimetic	↓PCP (by both short and long-term treatment with M40403)	
	Mice				
Palsson et al. 2007	NMRI, M	PCP	**L-Lysine** (subchronic; L-artinine transport inhibitor)	↓PCP	
Zhang et al. 2007a	Std:ddy, M	DIZ	**Minocycline** Second generation antibiotic	↓DIZ	

AChE acetylcholinesterase, *AMP* amphetamine, *APO* apomorphine, *ARI* aripipazole, *BN* Brown Norway, *BRO* bromocriptine, *CB* cannabinoid receptor, *β-CD* (2-hdroxypropyl)-beta-cyclodextrin, *CIR* cirazoline, *CLO* clozapine, *CORT* corticosterone, *DAAO* D-aminoacid oxidase, *DA* dopamine, *DAT* dopamine transporter, *DIZ* dizocilpine, *F* female, *GLU* glutamate, *GLY* glycine, *GLYT* glycine transporter, *HAL* haloperidol, *ICV* intracerebroventricular, *IR* isolation rearing, *KET* ketamine, *KYNA* kynuric acid, *LE* Long Evans, *LH* Lister hooded, *LSD* lysergic acid dyethylamide, *M* male, *MPEP* 2-methyl-*t*-(phenylethnyl)-pyridine, *MUS* muscarine, *NE* norepinephrine, *NET* norepinephrine transporter, *nHPC* neonatal hippocampus, *NOS* nitric oxyde synthase, *NT* neurotensin, *OLA* olanzapine, *OVX* ovariectomized, *ppm* parts per million, *PND* postnatal day, *PP* prepulse, *QUE* quetiapine, *QUI* quinpirole, *RAC* raclopride, *RIS* risperidone, *Rx* treatment, *SCO* scopolamine, *SD* Sprague Dawley, *SR* social rearing, *THC* tetrahydracannabinol, *TRP* transient receptor potential channel, *V* ventral, *VAN* vanilloid, *WI* Wistar, *WKYs* Wistar Kyoto, *WT* wild type, *ZIP* ziprasidone, ↓*XYZ* reduction of effect XYZ, ↑*XYZ* enhancement of effect XYZ, ∅XYZ no change of effect XYZ

Table 3 Model organisms, ca. 2001–2007

I. Low and high baseline PPI levels
II. Sub-strains selected by drug sensitivity
III. Genetically engineered organisms, based on genes related to:
- A. Vulnerability for schizophrenia
- B. Dopamine
- C. Glutamate
- D. Noradrenaline
- E. Histamine
- F. Catecholamines (general)
- G. Acetylcholine
- H. GABA
- I. Second Messenger Systems
- J. Neuropeptides
- K. Other
- L. Models for specific disorders

IV. Developmental models
- A. Isolation/Deprivation/Stress-related
  - 1. Isolation rearing
  - 2. Maternal deprivation
  - 3. Developmental stressors
  - 4. Immune-related
- B. Developmental drug exposure
- C. Developmental hypoxia
- D. Developmental nutritional deprivation
- E. Neonatal lesions

V. Drug-related models
- A. Drug withdrawal
- B. Toxin exposure

VI. Other

Superscript designates study-specific findings

References	Species, Strain, Sex	Model description/ background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
I. Low and high baseline PPI levels					
	Humans				
Bitsios et al. 2005[1]; Swerdlow et al. 2006a[2]; Vollenweider et al. 2006[3]	M	Basal PPI differences between subgroups ("low vs. high gaters")		∅PER, ∅AMA[1] in low gaters ↓PER[1], ↓AMA[1] in high gaters	QUE (↑PPI[2]), CLO (↑PPI[3]), both at short PP intervals and in low gaters; ∅PPI[3] in high gaters
	Rats				
Feifel and Priebe 2001[1]; Feifel et al. 2004[2]	BB, M	Basal PPI deficits	↓PPI[1,2]		CLO and PD 149 163 (a neurotensin mimetic; both ↑PPI), but HAL (∅PPI)[1,2]; subchronic HAL (↑PPI)[1]
Ferguson and Cada 2004[1]; van den Buuse 2004[2]	SHR vs. SD and WKY, M, F	SHR rats display behavioral abnormalities thought to model clinical symptoms	↓PA[1,2], ↓PPI relative to SD and WKY[1]; ↓PPI relative to SD (trend only)[2], but ∅PPI relative to WKY rats[2]	AMP (↓PPI in SHR and WKY, but ∅PPI in SD rats)[2]; APO (↓PPI in SD, but ∅PPI in SHR and WKY rats)[2]; DIZ , 8-OHDPAT (both ↓PPI in SHR, WKY, and SD)[2]	
Freudenberg et al. 2007	Former WI, M	Selective breeding of rats with high vs. low PPI			
Fujiwara et al. 2006	LEC and WI, M	A putative animal model of WD	↓PPI in LEC rats	CU (↓PPI in both LEC and WI rats)	

Table 3 (continued)

References	Species, Strain, Sex	Model description/ background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
II. Sub-strains selected by drug sensitivity					
	Rats				
APO Susceptibility					
Sontag et al. 2003[1]; van der Elst et al. 2006[2], 2007[3]	APO-SUS and APO-UNSUS, M	APO-SUS and APO-UNSUS rats were selectively bred to achieve high (SUS) vs. low APO (UNSUS) susceptibility	↓PPI in APO-SUS vs. APO-UNSUS rats[1,3] (not apparent in[2])	Sensitivity to the PPI-disruptive effects of COC[2] or AMP[3] (APO-SUS > APO-UNSUS)[2,3]	Removal of isolation stress: ↑PPI in APO-SUS, but ↓PPI in APO-UNSUS rats[1]; REMO (↓AMP in APO-SUS, but ∅AMP in APO-UNSUS)[3]; aMpT (depleted cytosolic DA, ∅PPI in both strains, ∅AMP in APO-SUS, ↓AMP in APO-UNSUS)[3], RES (∅PPI in both strains, ∅AMP in both strains)[3]; Tests in APO SUS only: REMO (∅PPI, ↓COC)[2], PRAZ (↑PPI, ↓COC)[2], KETS (↑PPI, ∅COC)[2], aMpT + RES (↓AMP)[3]
Alcohol preference					
Bell et al. 2003[1]; Ehlers et al. 2007[2]	F, M	Selective breeding of female rats or selection of male rats with high (P) vs. low (NP) alcohol preference	∅PPI after selective breeding;↑PPIinPrats[2]; ↓PPI in P rats housed in isolation[2]	Adult rats: AMP (↓PPI in P, but ↑PPI in NP rats); Adolescent rats: AMP (↓PPI in P, but ∅PPI in NP rats)	
III. Genetically engineered organisms, based on genes related to:					
A. Vulnerability for schizophrenia					
	Mice				
Clapcote et al. 2007	Missense mutations in exon 2 of the DISC1 gene	DISC1 is a proposed schizophrenia susceptibility gene	↓PPI in mice with missense mutation at residues 31L or 100P		CLO, HAL, BUP, Rolipram (PDE4 inhibitor; all ↑PPI; reversal of PPI was dependent on the specific type of missense mutation)
Barr et al. 2007	KO for reelin receptors VLDLR or APOER2, M, F	Reelin is reportedly reduced in brains of schizophrenia patients	∅ acoustic PPI in both KO, ↓ crossmodal PPI in VLDLR mice, ↑crossmodal PPI in APOER2 mice	PPI-disruptive effects of PCP: KO>WT	
Podhorna and Didriksen 2004	Heterozygous, reeler mutants, M, F	Reeler mice have a mutation in the gene for reelin and have been suggested as an animal model for schizophrenia	↓PPI only in fully adult F (trend only)		

Boucher et al. 2007	Heterozygous NRG1 KO, M	NRG1 is a proposed schizophrenia susceptibility gene	∅PPI	PPI-disruptive effects of THC: KO>WT	
Mukai et al. 2004	ZDHH8-KO, M, F	ZDHH8 is a proposed schizophrenia susceptibility gene	↓PPI in F, but ∅PPI in M		
B. Dopamine					
		DA receptors			
	Mice				
Ralph-Williams et al. 2002	D1-KO, or D2-KO, M, F		∅PPI in D1-KO, but ↓PPI in D2-KO	APO, SKF82958 (both ∅PPI in D1-KO, but ↓PPI in WT; ↓PPI in D2-KO and WT); AMP (↓PPI in D1-KO and WT, ∅PPI in D2-KO, but ↓PPI in WT); DIZ (↓PPI in D1-KO, D2-KO, and WT)	
Holmes et al. 2001	DA D5 null mutants, M, F		∅PPI	SKF 81297 (∅PPI in mutants, but ↓PPI in WT)	
		DAT			
	Mice				
Barr et al. 2004[1]; Yamashita et al. 2006[2]	DAT-KO, M	Increase dopamine activity has been proposed in schizophrenia	↓PPI[1,2]	COC, METP (both ↑PPI in KO, but ↓PPI in WT)[2]	M100907 ($5\text{-}HT_{2A}$ antagonist, ↑PPI in KO, but ∅PPI in WT)[1]; FLX, NSX (a NET inhibitor, both ↑PPI in KO, but ∅PPI in WT)[2], CIT (∅PPI in KO and WT)[2]
Ralph-Williams et al. 2003b	DAT-knock-downs, M, F		∅PPI		
		Other Dopamine related			
Eells et al. 2006	**Mice**, nuclear receptor Nurr1 null mutants	Nurr1 is important for development of DA neurons; early postnatal isolation	↓PPI after postnatal isolation in Nurr1$^{+/-}$ mice		
C. Glutamate					
		NR1			
	Rats				
Inada et al. 2003	WI, M	Antisense knock-down of HPC NR1 by HPJ-liposome vector	↓PPI		
	Mice				
Bickel et al. 2008[1]; Duncan et al. 2004[2], 2006a[3]; Moy et al. 2006[4]	TG with reduced expression of NR1, M, F	NMDA receptor signaling may be reduced in schizophrenia. Microtubule stabilization in neurons depends on STOP	↑PA[1,2,3,4], ↓PPI[1,2,3,4]	Sensitivity to PPI-disruptive effects of AMP: TG>WT[4]	HAL, CLO, RIS (all ↑PPI in both TG and controls)[3]
Fradley et al. 2005	TG with reduced expression of NR1 or STOP-KO, M, F		↓PPI (in both mouse types)		CLO (∅PPI in both mouse types)

Table 3 (continued)

References	Species, Strain, Sex	Model description/ background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
		NR2			
	Mice				
Boyce-Rustay and Holmes 2006[1]; Spooren et al. 2004[2]	NR2A-KO, M, F		∅PPI[1,2]	Ro 63-1908 (a selective NR2B receptor antagonist,↓PPI)[2]	
Takeuchi et al. 2001	NR2A, NR2B, N2C, N2D, or GLURδ2 mutants	NR2A-D are known subunits of the NMDA receptor channel. GLURδ2 is a relatively novel GLU receptor subunit	↑PA in NR2A, B, C and D mutants, ∅PAin GLURδ2, ↑PPI in NR2B and GLURδ2, ∅PPI in NR2A, C and D		
		NR3			
Brody et al. 2005	**Mice** NR3A-KO or TG NR3A overexpressors, M, F		↑PPI at 3–4 weeks old M, but ∅PPI in FKO; ∅PPI in TG		
		AMPA			
Wiedholz et al. 2008	**Mice**, AMPA GLUR1-KO, M, F	The gene encoding GLUR1 lies within a chromosomal region that is associated with schizophrenia	↓PPI		
		mGLU			
	Mice				
Brody et al. 2003a, b	mGLU1-KO, M	Reduced glutamate function has been proposed in schizophrenia	↓PPI[1,2,3]	PCP (↓PPI in KO and WT)	RAC (∅PPI in KO and WT), LAM (↑PPI in KO and WT)
Brody and Geyer 2004b[1]; Brody et al. 2004a[2]; Lipina et al. 2007[3]	mGLU5-KO, M, F		↓PPI	PPI deficit of KO mice could not be mimicked in WT mice with the mGLU5 antagonist MPEP[1], no further disruption of PPI by DIZ in KO[3]	RAC, CLO, LAM (all ∅PPI)[2], CX546 and ARIR (positive modulators of AMPA, both ↑PPI (less pronounced with ARIR))[3]
		Other glutamate related			
	Mice				
Szumlinski et al. 2005	Homer1-KO or Homer2-KO, M, F	Homer proteins interact with mGLU, and modify the morphology of GLU synapses. A SNP in Homer1 was associated with schizophrenia	↓PPI in Homer1-KO, but ∅PPI in Homer2-KO		HAL (↑PPI in Homer1-KO)
Tsai et al. 2004	Heterozygous GLYT-KO, M	GLY is a co-agonist at the NMDA-receptor with presumed sub-saturating concentrations at the receptor	∅PPI	Sensitivity to the PPI-disrupting effects of AMP (KO < WT) or DIZ (KO > WT)	

Wolf et al. 2007	CPB-K vs. Balb, M	CPB-K mice display low levels of NMDA receptors	↑PA, ↓PPI relative to BalbC mice		Acute or subchronic CLO (∅PPI)
D. Noradrenaline					
Lahdesmaki et al. 2004	**Mice**, adrenergic α_{2A}-KO, M, F	Adrenergic α_{2A} receptors modulate transmitter release of DA and 5-HT neurons	↑PPI	AMP (↓PPI in KO, and WT; greater sensitivity to AMP in KO), DEXM (an α_2 agonist, ∅PPI, ↓AMP in KO, but not WT)	ATI (an α_2 antagonist, ∅PPI, ∅AMP)
E. Histamine					
Dai et al. 2005	**Mice**, H1-KO, M	Histaminic abnormalities have been implicated in the pathophysiology of schizophrenia	↓PPI in WT, but ∅PPI in KO after IR		Sensitization to METH enhanced effects of IR on PPI in WT, but not in KO mice
F. Cathecholamines (General)					
Klejbor et al. 2006	**Mice**, FGFR1-TG, M, F	FGFR1-TG express a dominant-negative mutant from the catecholaminergic, neuron-specific TH promoter	↑PA, ↓PPI		FLUP (a DA antagonist, ↑PPI)
G. Acethylcholine (ACh)					
		Nicotinic			
	Mice				
Bowers et al. 2005	Nicotinic α7-KO, M	Evidence suggests reduced α7 expression in schizophrenia patients	∅PPI	PPI-disruptive effects of EtOH: KO=WT	
Cui et al. 2003	Nicotinic β3-KO, M, F	β3-subunit of the nACH is highly expressed in DA neurons of the SN and VTA	↓PPI		
		Muscarinic			
Thomsen et al. 2007	Mice, M5-KO, M, F	The M5 muscarinic ACh receptor has been implicated in susceptibility to schizophrenia	↓PPI	AMP (↓PPI in KO and WT)	CLO (↑PPI in KO, but ∅PPI in WT; ∅AMP in both KO and WT), HAL (↑PPI in KO and WT; ↓APO in both KO and WT)
H. GABA					
		$GABA_A$			
	Mice				
Hauser et al. 2005	$GABA_A$ α5 mutants, M, F	The α5 subunit of the $GABA_A$ channel is strongly expressed in the HPC	↓PPI		
Yee et al. 2005	$GABA_A$ α3-KO, M, F	The α3-$GABA_A$ receptor is the main receptor subtype expressed by GABA-ergic neurons involved in controlling monoaminergic neurons	↓PPI		HAL (↑PPI)

Table 3 (continued)

References	Species, Strain, Sex	Model description/ background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
		Other GABA related			
	Mice				
Chiu et al. 2005	GAT1-KO, M, F	GAT1-KOs display behavioral abnormalities proposed to model some aspects of psychopathology	↓PPI		
Heldt et al. 2004	GAD65-KO, M, F	GAD65 is a GABA synthesizing enzyme	↓PPI		CLO reversed the PPI deficit of KO
I. Second messenger systems					
	Mice				
Gould et al. 2004[1]; Kelly et al. 2007[2]	TG with a constituitively active $G_s\alpha$ or TG with R(AB), or $G_s\alpha$ x PKA double TG mice, M, F	R(AB) TG express a PKA type inhibitor. G-protein signaling related to the cAMP/PKA pathway may be abnormal in schizophrenia	↓PPI in $G_s\alpha$ TG, but ∅PPI in PKA TG[1,2] and $G_s\alpha$ x R(AB) double TG[2]		HAL (↑PPI in $G_s\alpha$ TG, but ∅PPI in R(AB) TG), ROL (↑PPI in $G_s\alpha$ TG)[2]
Harrison et al. 2003	LAP1, M, F	LAP1 is a G-protein coupled receptor with developmental expression suggesting a role in psychopathology	↓PPI		
Koh et al. 2008	PLCβ1-KO, M, F	PLCβ1 may be altered in brains of schizophrenia patients	↓PPI		HAL (↑PPI in KO, but ∅PPI in WT)
Shum et al. 2005	CaMKIV-KO, M	CaMKIV is thought to be involved in neuroplasticity and aspects emotional behavior	↓PPI (and ↓PA)		
van den Buuse et al. 2005a	$G_z\alpha$-KO, M	$G_z\alpha$ is a G-protein of the Gi type and associated with DA D2-receptors	∅PPI	Sensitivity to the PPI disruptive effects of AMP, APO (both: KO>WT) or DIZ (KO=WT)	
J. Neuropeptides					
		Neurotensin			
	Rats				
Caceda et al. 2005	M	Virally mediated over expression of NT1 in the NAC	∅PPI	↓AMP, ↓DIZ	
	Mice				
Kinkead et al. 2005	NT null mutants, M, F	NT is proposed to have “endogenous antipsychotic” properties	↑PA, ↓PPI	AMP (∅PPI in mutants, but ↓PPI in WT)	HAL, QUET (both ∅PPI in mutants, but ↑PPI in WT), CLO (↑PPI in mutants and WT), OLA (∅PPI in mutants amd WT)

		CRF			
	Mice				
Dirks et al. 2002[1], 2003[2]; Groenink et al. 2008[3]	TG CRF1 overexpressors, M	CRF abnormalities may play a role in psychopathology	↓PPI[1,2,3]		CRF1 antagonists (↑PPI in TG, but ∅PPI in WT), GR antagonists (∅PPI in TG and WT), adrenelectomy (∅PPI in TG and WT)[3]; HAL, CLO, RIS, but not CDP all reduce PPI deficit of TG relative to WT
Risbrough et al. 2004	CRF1-KO, M		∅PPI	CRF (↑PPI in KO, but ↓PPI (and ↑PA) in WT)	
		Arginine Vasopressin			
Egashira et al. 2005	**Mice**, V1b-KO, M	V1b plays a role in regulation of the physiological response to stress	↑PA, ↓PPI		CLO, RIS (both ↑PPI), but HAL (∅PPI)
		Gastrin			
van den Buuse et al. 2005b	Gastrin-KO, M	Gastrin is a peptide hormone. It is also produced in the brain and binds to the CCK receptor. CCK interacts with DA in the brain	∅PPI	Sensitivity to the PPI-disruptive effects of AMP (KO<WT), but for APO, DIZ, 8-OHDPAT (all KO=WT)	
		Neurexin			
Beglopoulos et al. 2005	**Mice**, Nxph3-KO, M	Nxph3 is a ligand of synaptic α-neurexins	↑PA, ↓PPI		
		PACAP			
Tanaka et al. 2006	**Mice**, Adcyap1-mutants	Adcyap1 mutants lack the gene encoding for PACAP and display marked behavioral abnormalities including hyperlocomotion and jumping behavior	↓PPI	AMP (↑PPI)	HAL (∅PPI)
K. Other					
Wang et al. 2003a, b	**Mice**, adenosine A_2-KO, M	Adenosine may influence PPI by interacting with the DA system of the brain	↓PA, ↓PPI	AMP (∅PPI in KO and WT (slight trend towards ↓PPI in KO, but ↑PPI in WT); DIZ (↓PPI in KO and somewhat more pronounced in WT)	
Wolinsky et al. 2007	**Mice**, TA1-KO, M	Trace amines have been implicated in schizophrenia	↓PPI		
	Mice				
Gogos et al. 2006[1]; van den Buuse et al. 2003[2]	Aro-KO, M, M (castrated), F	Gender differences in psychiatric disease; aromatase converts testosterone into estrogen	∅PPI in M, castrated M, and F[1]; age-dependent ↓PPI in M, but ∅PPI in F (slight trends only)[2]	PPI-disruptive effect of 8-OHDPAT (F K0=F WT; M KO>M WT; enhanced in castrated M WT, but not in KO)[1]	

Table 3 (continued)

References	Species, Strain, Sex	Model description/background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
Weil et al. 2006	MT1-KO, M, F	Melatonin has been implicated in psychiatric disease	↓PPI		
	Mice				
Petitto et al. 2002a	Double deletion of IL2/IL15Rβ-double-KO, M, F	IL2 and IL15 are cytokines that share a common β-receptor subunit, which is essential for intracellular signaling. Expression levels are high in HPC and limbic regions	↓PA, ↓PPI		
Petitto et al. 2002b	MRL-lpr substrain, M	MRL-lpr mice develop lupus-like autoimmune disease, but also reduced IL2 production. Schizophrenia may involve immune processes of the CNS	∅PPI in pre-disease MRL-lpr, but ↓PPI with evidence of autoimmune disease		
	Mice				
Irintchev et al. 2004	L1 or CHL1, M, F	The cell-adhesion molecule L1 and its close homologue CHL1 may be linked to schizophrenia	↓PPI		
Jaworski et al. 2005	TIMP-2-KO or knock-down, M, F	TIMP influence extracellular matrix molecules and may be involved in brain plasticity and possibly brain development	↓PPI in KO when comparedto heterozygous,butnot knock-downorWT animals		
Pillai-Nair et al. 2005	NCAM-TG, M, F	NCAM is elevated in brains from schizophrenia patients	↓PPI		CLO (↑PPI), HAL (∅PPI)
	Mice				
Brunskill et al. 2005[1]; Erbel-Sieler et al. 2004[2]	Npas1-KO, Npas3-KO, M, F	Npas is a transcription factor highly expressed in developing neuroepithelium	↓PPI in Npas1[2] and Npas3[1,2]-KO		
Burne et al. 2005	Vitamin D receptor KO, M, F	Vitamin D contributes to normal brain development.	↓PPI at long PP intervals		
Cao and Li 2002	Emx1 mutants, M, F	Emx1 is implicated in forebrain development and behavioral processes.	(↓PPI; trend only)		
McDonald et al. 2001	FGFR3-null mutants, M, F	FGFR may contribute to neuronal growth, angiogenesis, mitagenesis and skeletal development	↓PPI		

Miyakawa et al. 2003	CN-mutants, M	CN is involved in neurite extension and neuronal plasticity. CN-mutants display behavioral abnormalities	↓PPI
Park et al. 2002	CDF mutants and Catna2-TG (of CDF mutants)	CDF-mutants show morphological abnormalities in the HPC and cerebellum as well as behavioral abnormalities. Catna2-TG have partially restored CDF regions and normal HPC and cerebellum morphology	↓PPI in CDF-mutants; ∅PPI in Catna2-TG
Porras-Garcia et al. 2005	Heterozygous Lurcher mutants, M	Lurcher mutants display a progressive loss of Purkinje neurons	↓PPI
Yukawa et al. 2005	STAT6-deficient, M	STAT6 is expressed in the CTX, HPC, striatum (developing brain), and basal forebrain (adults). STAT are signaling molecules that mediate cytokine-related mechanisms	↓PPI
L. Models for specific disorders			
		Fragile X-syndrome	
	Humans + mice		
Frankland et al. 2004[1]; Spencer et al. 2006[2]	Human children with FXS, Fmr1-KO, Fmr2, or Fmr1+2 double KO mice, M	Fmr-KO mice are putative animal models of FXS	↓PPI in children with FXS[1] and in Fmr1-KO[1], but ∅PPI in Fmr1-KO[2] and FMR1+2 double KO[2]
Bontekoe et al. 2002	FXR2-KO, M	FXR2 is a homolog of the FMRP protein, which is lacking or mutated in FXS.	↓PPI
Chen and Toth 2001	FMR1-KO, M	FMR1-gene encodes the FMRP protein, which is lacking or mutated in FXS.	↑PPI
		Nasu-Hasu-Hikala disease	
Kaifu et al. 2003	**Mice**, DAP12-deficient, M, F	DAP12 deletions lead to the Nasu-Hikala disease	↓PA, ↓PPI
		22q11 deletion syndrome	
Paylor et al. 2006	**Mice**, with chromosomal deletions Df1, 2, 3, 4 or 5, or mutations of genes Tbx1, Gnb1l, or Cdcrel1, M, F	Chromosomal Df1 deletions are a putative animal model of 22q11 deletion syndrome, which is linked to high schizophrenia rates. Df1	↓PPI in mice with deletions of Df1, Df2, Df3 and mutations of TbX1, Gnb1l. ∅PPI in mice with deletions of

Table 3 (continued)

References	Species, Strain, Sex	Model description/ background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
		deletions were "behaviorally mapped" to mutations of single genes via PPI	Df4 or Df5, and mutations of Cdcrel1		
		Huntington's disease			
Van Raamsdonk et al. 2005	**Mice**, YAC128	HD patients have motor-, cognitive- and psychiatric disturbances. YAC128 mice express mutant huntingtin and are a presumed animal model for HD	↓PPI in older mice		
		Alzheimer's disease			
	Mice				
Ewers et al. 2006	APP&PS1 double-KO, M, F	AD involves neuropathological changes in the HIP	∅PPI, but correlation between PPI deficits and neuropathological changes		
McCool et al. 2003	CRND8-TG, M	CRND8-TG show over expression of Swedish/ Indiana familial mutations of APP and an age dependent increase of amyloid production	↓PPI (small effects)		
Taniguchi et al. 2005	WILD and N279K mutants, M, F	TAU mutations may play a causal role in forms of dementia and PD. N279K and WILD mutants contain a mutation of the human TAU gene	↓PPI in N279K mutants, ∅PPI in WILD mutants		
IV. Developmental models					
A. Isolation/deprivation/stress-related					
1. Isolation Rearing					
	Rats				
Barr et al. 2006[1]; Cilia et al. 2005[2]; Day-Wilson et al. 2006[3]; Harte et al. 2007[4]; Powell et al. 2002[5], 2003[6]; Rosa et al. 2005[7]	SD, FLH, M; LE, M; WI, M	IR	↓PPI in M and F, and all strains [1,2,3,4,5,6,7]	Water deprivation (∅PPI)[5]	Iloperidone (broad spectrum DA/5-HT/NE antagonist, maternal dep 3. ∅PPI)[1]; compound A (α7 agonist, ↑PPI[2]); DA-depletion with 6-OHDA (↑PPI)[6]; handling (↑PPI)[7]
Nunes Mamede Rosa et al. 2005	WI, M	Post-weaning isolation for 10 days	↑PPI (not reversed by resocialization)		

	Mice				
Dai et al. 2004[1], 2005[2]; Sakaue et al. 2003[3]; Varty et al. 2006[4]	C57, ddY, 129 and H_1-KO, all M	IR	↓PPI in WT mice [1,2,3]; ↓PPI (C57and129micein atleastoneofthetwotest sessions)[4] ∅PPI in H1-KO[2]		Sensitization to AMP enhanced effects of IR on PPI in WT[1,2] but not in H1-KO[2], RIS and MKC-242 (a 5HT1a agonist, both ↑PPI)[3]
2. Maternal deprivation					
	Rats				
Choy and van den Buuse 2007		Early stress: MD. Later stress: implantation of CORT pellets	↓PPI (trend only in MD rats)	APO (↓PPI in CTR and rats treated with either MD or CORT, but ∅PPI in rats exposed to MD and CORT); AMP (↓PPI in CTR, but ∅PPI in rats exposed to MD); 8-OHDPAT (↓PPI in all groups)	
Ellenbroek and Cools 2002	WI, M, nulliparous F	IR, MD, rearing by MD mother	↓PPI in IR rats; ↓PPI in MD rats; ∅PPI in MD +IR rats; ↓PPI in pups reared by a MD mother; ↓PPI in MD pups reared by a non-MD mother		
Garner et al. 2007	WI, F	Early stress: MD. Later stress: Implantation of CORT pellets	↓PPI in MD rats, ∅PPI in CORT treated rats		
Husum et al. 2002	WI, M	MD	↓PPI		
3. Developmental stressors					
	Rats				
Hauser et al. 2006	WI, M, F	Prenatal DEX exposure	↑PPI in M (not replicated in a second study)		
Koenig et al. 2005	SD, M	Exposure of pregnant females to stressors	↓PPI		
Burton et al. 2006[1]; Lovic and Fleming 2004[2]	SD, M, F	Exposure of pregnant females to restraint stress or exposure of offspring to AR with or without mechanical stimulation	∅PPI in response to restraint condition[1]. ↓PPI after AR with minimal stimulation[1,2], but ∅PPI after AR with maximal stimulation[2]		
Iso et al. 2007	**Mice**, C57, M	Animals were exposed to enriched or impoverished conditions during development	↓PPI in mice continuously kept in impoverished conditions		
4. Immune-related					
	Rats				
Borrell et al. 2002[1]; Romero et al. 2007[2]	WI, M, F	Prenatal bacterial immune challenge with LPS	↓ acoustic PPI in M rats [1,2], ↓ visual PPI in F rats[2]		HAL, CLO (both ↑PPI in M and F)[1]; chronic HAL (↑PPI)[2]

Table 3 (continued)

References	Species, Strain, Sex	Model description/ background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
Fortier et al. 2007	SD, M	Prenatal (or postnatal) systemic bacterial (LPS), viral (poly I:C) or local (TUR) immune challenge	LPS (↓PPI at E15-16 and E18-19); poly I:C (∅PPI); TUR (↓PPI at E15-16)		
Pletnikov et al. 2002	Lewis or Fisher, M	IC-infusion of BDV on PND0	↓PPI in Fisher rats, but ∅PPI in Lewis rats		
	Mice				
Nyffeler et al. 2006[1]; Ozawa et al. 2006[2]	C57, M, F; Balb, M, F	Prenatal viral (poly I:C) immune challenge	↓PPI in adults, but ∅PPI in Balb juveniles[2]. Correlation between immunoreactivity for α2 $GABA_A$ immunoreactivity in the ventral dentate gyrus and PPI in CTR, but not in immune-challenged C557 mice[1]		
Rajakumar et al. 2004	SD, M	IC-injection of antibody against the p75 neurotrophin receptor at PND0 to suppress neurotrophin activity	↓PPI		
Shi et al. 2003	Balb or C57, M, F	Prenatal systemic immune challenge with influenza or poly I:C virus	↓PPI under both conditions		CLO, CHLO (both ↑PPI following challenge with influenza virus)[1]
B. Developmental drug exposure					
	Rats				
Tan 2003	WI, M, F	Exposure to AMP or vehicle during pregnancy (GD8 to parturition) followed by an acute AMP or vehicle exposure challenge on the day of testing	↓PPI and ↑PA after prenatal AMP treatment		
Harris et al. 2003	SD, M, F	Neonatal DIZ exposure	↓PPI in F, but ∅PPI in M		
Rasmussen et al. 2007	SD, M, F	Neonatal PCP or vehicle exposure on PND 7, 9 and 11 followed by a single PCP or vehicle exposure at PND45. Rats were tested at PND32-34 and 1,4 and 6 weeks after the PND45 treatment	∅PPI after neonatal PCP treatment only; transient ↓PPI after neonatal + adolescent PCP; ↑PPI in F, but ∅PPI in M after adolescent PCP only		

Takahashi et al. 2006	WI, M, F	Daily exposure to PCP over 2 weeks in neonatal vs. adult rats	Persistent ↓PPI after neonatal PCP treatment, in M and F, transient ↓PPI after adult PCP administration in M		
Wang et al. 2003a	SD	Neonatal PCP or vehicle exposure on PND 7, 9 and 11	↓PPI		M40403 (a SOD mimetic, ∅PCP after short term treatment, but ↓PCP after long term treatment)
Slawecki and Ehlers 2005	SD, M	Alcohol exposure during adolescence or adulthood	↑PPI after adolescent exposure, but ∅PPI after adult exposure (↓PA for both groups)		
Schneider and Koch 2003[1]; Schneider et al. 2005[2]	WI, M	Chronic prepubertal, pubertal, or adult exposure to the CB agonist WIN 55,212-2	↓PPI in prepubertal[2] and pubertal[1] rats, but ∅PPI in adult[1] rats		HAL (↑PPI)[1,2]
Schneider et al. 2006	WI, M	Prenatal valproate exposure	↓PPI		Environmental enrichment (↑PPI)
Gizerian et al. 2006[1]; Grobin et al. 2006[2]	SD, M, F	Neonatal ALO administration on PND2 or PND5 or PND1 and PND5	↓PPI at PND 80[1,2] and 20[2], but not at PND 40[2] and 60[2]		CLO (↑PPI in the ALO PND2 group; ∅PPI in the PND5 group)[1]
Watanabe et al. 2004	SD, M	Cytokines have been implicated in the pathophysiology of schizophrenia. Neonatal challenge with the cytokine LIF from PND2 to PND10	↓PPI during and after adolescence		
Futamura et al. 2003[1]; Sotoyama et al. 2007[2]	SD, M, F	Neonatal perturbation of neurotrophic signaling via EGF administration	↑PA[1,2], ↓PPI[1,2]	Sensitivity to the PPI-disruptive effects of subthreshold APO or QUIN in EGF-treated rats > controls; SKF38393 (∅PPI)[2]	Subchronic CLO (↑PPI), but subchronic HAL (∅PPI)[1]
Henck et al. 2001	WI, M, F	Neonatal exposure to supraphysiological doses of the mitogen EGF	↓PPI in F, but ∅PPI in males		
	Mice				
Thomsen et al. 2007	DBA, C57, C3H, ddyY, M, F	Neonatal EGF administration	↑PA for all strains, ↓PPI in DBA and C57, but ∅PPI in C3H and ddyY mice		
	Rats				
Elmer et al. 2004	SD, M	Prenatal challenge with antimitotic Ara-C.	↓PA, ↓PPI in post-adolescent rats	APO (∅PPI)	
Jongen-Relo et al. 2004[1]; Le Pen et al. 2006[2]	WI, F, M; SD, M	Prenatal challenge with antimitotic MAM (at different time points during pregnancy)	↓PPI in M SD rats [2], (↓PPI for specific PP and PND of MAM challenge in WI rats, trend only)[1]		

Table 3 (continued)

References	Species, Strain, Sex	Model description/background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
Shishkina et al. 2004	WI, M	Neonatal short-term reduction of brainstem α2 adrenergic receptors via injection of antisense oligonucleotides	↓PPI at PND 34, but ∅PPI at PND 22 and 80		
Howland et al. 2004a	**Rats**, LE, M	Neonatal i.p. injections of KA	↓PPI	Sensitivity to the PPI-disruptive effects of APO in KA-treated rats = controls	
C. Developmental hypoxia					
	Guinea pigs				
Rehn et al. 2004	DH, Dunkin-Hartley, F	Reduction in utero-placental blood flow via unilateral ligation of the uterine artery	↓PPI		
	Rats				
Tejkalova et al. 2007	WI, M	Hypoxia on PND12 via bilateral carotid arterial occlusion	↓PPI		
Sandager-Nielsen et al. 2004	SPF-WI, M	Anoxia on PND9	(↓PPI in 1 of 2 experiments only)	AMP(↓PPItolowdose,trend only)	
Schmitt et al. 2007	SD, M	Repeated mild hypoxia from PND4-8	↓PPI		
D. Developmental nutritional deprivation					
	Rats				
Burne et al. 2004	SD, M, F	Pre- and postnatal vitamin D deprivation.	↓PPI only after combined pre- and chronic postnatal vitamin D deficiency		
Palmer et al. 2004	WKY, M, F	Prenatal protein deprivation. Prenatal malnutrition may increase the risk for schizophrenia	↓PPIinFatPND56,but ∅PPIatPND35;∅PPIin M		
E. Neonatal lesions					
	Rats				
Daenen et al. 2003	WI, M	Neonatal IA-lesion of the vHPC or AMY	↓PPI in adult rats lesioned at PND7, ∅PPI in adult rats lesioned at PND21		
Laplante et al. 2005[1]; Powell et al. 2006; Le Pen and Moreau 2002[2]; Le Pen et al. 2003[2]; Rueter et al. 2004[4]; Zhang et al. 2006[5]	SD, M	Neonatal IA-lesion of the vHPC	↓PPI in lesioned post-pubertal rats[1,2,3,4,5]	OXO (a muscarinic agonist, ∅PPI in lesioned rats, but ↓PPI in non-lesioned rats)[1]	HAL (∅PPI in lesioned rats and ↓PPI in non-lesioned rats[2], but ↑PPI in lesioned rats and ∅PPI in non-lesioned rats)[5], CLO and OLA (↑PPI in lesioned rats, ↓PPI in non-lesioned rats)[2], RIS[2], BIP[1] (a muscarinic

					antagonist), GLY[3], and ORG 24598[3] (a NMDA co-agonist, all ↑PPI in lesioned rats, ∅PPI in non-lesioned rats)[3]; chronic CLO or RIS (↑PPI); BP 897, AVE 5997, A-437203 (all preferential D3 antagonists, ∅PPI)[5]
Schneider and Koch 2005	**Rats**, WI, M	Neonatal IA-lesion of the mPFC. Morphological changes in the mPFC in schizophrenia patients have been reported	↑PPI after neonatal lesion in juvenile rats, but ∅PPI in adult rats	Sensitivity to the PPI-disruptive effects of APO in adults: lesioned > non-lesioned	
Schwabe et al. 2004	**Rats**, WI, M	Neonatal or adult IA-lesion of the mPFC	↑PPI in adult rats after neonatal lesion, but ∅PPI after adult lesions	APO (↓PPI)	
V. Drug-related models					
A. Drug withdrawal					
	Rats				
Peleg-Raibstein et al. 2006a[1], b[2]; Tenn et al. 2003[3]	WI, M, SD, M	Withdrawal from repeated, escalating AMP administration schedules (up to 5 mg/kg, 8 mg/kg, or 10 mg/kg). The endogenous DA system of unmedicated schizophrenia patients has been hypothesized to be “sensitized”	∅PPI with up to 5mg/kg AMP in WI[1], but ↓PPI in SD[3]; ↓PPI under all other conditions		
Wilmouth and Spear 2006	SD, M	Withdrawal from nicotine (7 days of exposure). Withdrawal was induced by mecamylamine after nicotine treatment	↓PPI in adolescents on day 1, but ∅PPI on day 4 of withdrawal. ∅PPI at either day in adults		
B. Toxin exposure					
	Rats				
Terry et al. 2007	SD, M	Chronic, intermittent exposure to the organophosphate pesticide chlorpyrifos	↓PPI		
Tadros et al. 2005	WI, M	Repeated injection of the mitochondrial toxin 3-NP leads to selective striatal lesions and behavioral changes linked to HD	↓PPI (↓PA)		TAUR (a semi-essential β-amino acid, when administered prior to 3-NP: ↓3-NP)
VI. Other					
	Rats				
Pijlman et al. 2003	WI, M	Exposure to physical stress (PS, foot shock) or emotional	↑PPI in PS, but ∅PPI in ES rats		

Table 3 (continued)

References	Species, Strain, Sex	Model description/ background/rationale	Basal PPI	Effects of drugs typically used to induce PPI deficits	Effects of (presumed) antipsychotics/other treatments
		stress (ES, witness of foot shock to PS rat)			
	Mice				
van den Buuse et al. 2004	C57, M	ADX. CORT replacement. Stress is a risk factor in psychiatric disease	∅PPI (for ADX, ADX+CORT)		HAL (↑PPI in ADX+CORT and CTRL mice, but ∅PPI in ADX mice)
	Rats				
Byrnes et al. 2007	SD, F postpartum rats	Postpartum female rats	∅PPI	Sensitivity to the PPI-disrupting effects of QUIN: Postpartum rats < controls	
	Mice				
Tremolizzo et al. 2005	BtC3Fe, M	Hypermethylation may be related to downregulation of Reelin and GAD67 in schizophrenia patients. Methionine exposure for 2 weeks is used as an epigenetic model for schizophrenia	↓PPI		Chronic VAL (↓Methionine), acute IMID (↓Methionine)

ACH Acetylcholine (receptor), *AD* Alzheimer's disease, *ADX* adrenalectomy, *ALO* allopregnanolone, *AMA* amantadine, *AMP* amphetamine, *aMpT* alpha-methyl-para-tyrosine, *AMY* amygdala, *APP* amyloid precursor protein, *AR* artificial rearing, *ARIR* ariracepam, *APO* apomorphine, *ATI* atipamezole, *BB* Brattleboro, *BDV* Borna Disease virus, *BIP* biperiden, *BUP* bupropion, *CaMKIV* Calcium–calmodulin-dependent protein kinease IV, *CCK* cholecystokinin, *CB* cannabinoid (receptor), *CDP* chlordiazepoxide, *CHLO* chlorpromazine, *CIT* citalopram, *CLO* clozapine, *CNS* central nervous system, *COC* cocaine, *CORT* corticosterone, *CRF* corticotropin releasing factor, *CTR* controls, *CU* copper, *DA* dopamine (receptor), *DAT* dopamine transporter, *DEX* dexamethasone, *DEXM* dexmedetomidene, *DIZ* dizocilpine, *E* embryonic day, *EGF* epidermal growth factor, *F* female, *FGFR* fibroblast growth factor receptor, *Fmr1* fragile X mental retardation 1 gene, *FLUP* flupenthixol, *FLX* fluoxetine, *FXS* Fragile X syndrome, *GAD* glutamic acid decarboxylase, *GAT* GABA transporter, *GD* gestation day, *GR* glucocorticoid receptor, *GLU* glutamate, *GLY* glycine, *H* histamine (receptor), *HAL* haloperidol, *HD* Huntington's disease, *HPC* hippocampus, *IMID* imidazenil, *KA* kainic acid, *KETS* ketanserin, *KO* knock-out, *LAM* lamotrigine, *LAP* lysophosphatidic acid receptor, *LE* Long–Evans rat, *LEC* Long–Evans Cinnamon rat, *LIF* leukemia inhibitory factor, *LPS* lipopolysaccharide, *M* male, *m* metabotropic, *MAM* metholazoxymethanol acetate, *MD* maternal deprivation/maternally deprived, *MT* melatonin (receptor), *n* nicotinic, *METH* metamphetamine, *METP* methylphenidate, *NAC* nucleus accumbens, *NBM* nucleus basalis magnocellularis, *NCAM* neural cell adhesion molecule, *NET* norepinephrine transporter, *3-NP* 3-nitropropionic acid, *NR* NMDA receptor subunit, *NRG* neuregulin, *NSX* nisoxetine, *NT* neurotensin, *Nxph* neurexophilin, *OLA* olanzapine, *OXO* oxotremorine, *PA* response to pulse alone, *PACAP* pituitary adenylate-cyclase-activating polypeptide, *PD* Parkinson's disease, *PND* postnatal day, *PER* pergolide, *PLC* phospholipase C, *poly I:C* polyinosinic:polycytidylic acid, *PRAZ* prazosin, *PS1* presinilin1, *QUET* quetiapine, *QUIN* quinpirole, *RAC* raclopride, *REMO* remoxipride, *RIS* risperidone, *ROL* rolipram, *ROP* ropinirole, *SD* Sprague–Dawley rat, *SHR* spontaneously hypertensive rat, *SN* substantia nigra, *SOD* superoxide dismutase, *STAT* signal transducers and activators of transcription, *SUS* susceptible, *TA* trace amine (receptor), *TAUR* taurine, *TG* transgenic, *TH* tyrosine hydroxylase, *THC* tetrahydrocannabinol, *TIMP* tissue inhibitor of metalloprotease, *TUR* turpentine, *UNSUS* unsusceptible, *VAL* valproate, *VTA* ventral tegmental area, *V1b* Vasopressin receptor 1b, *WD* Wilson's Disease, *WI* Wistar rat, *WKY* Wistar–Kyoto rat, *WT* wild-type, ↓ decreased, ↑ increased, ∅ unchanged

Table 4 Examples of studies providing anatomically-specific information regarding the neural substrates of PPI, ca. 2001–2007

I. Nucleus accumbens	VI. Dorsomedial thalamus	X. Inferior Colliculus
II. Hippocampus	VII. Habenula	XI. Pedunculopontine nucleus
III. Prefrontal cortex	VIII. Medial septum	XII. Laterodorsal tegmental nucleus
IV. Entorhinal cortex	IX. Nucleus Basalis of Meynert	XIII. Raphe complex
V. Amygdala		XIV. Brainstem

Reference	Rat strain, sex	Brain regions	Manipulation	Effect on PPI
		I. NAC		
			Adults	
Cacedaetal. 2005	LE, M		Virally mediated increase in NT1 receptor	Blocked AMP & DIZ-induced PPI deficits
Culm et al. 2003	SD, M		Infusion of PTX	Blocked QUIN-induced PPI deficit
Culm et al. 2004	SD, M		Infusion of Sp-cAMP	Blocked QUIN-induced PPI deficit
Mohr et al. 2007	Mice, C3H, F		Infusion of DIH or QUIN	↑ PPI after QUIN, but ∅ PPI after DIH
Nagel et al. 2003	SD, M		Infusion of MSX-3 (A2 antagonist)	↓ PPI
Pothuizen et al. 2005	WI, M	Core, shell	Infusion of muscimol	Loss of PP intensity dependency after infusion into NAC core but not shell
Pothuizen et al. 2006	WI, M	Core	NMDA-lesion of the NAC core	enhanced PPI disruption by DIZ but not APO
Powell et al. 2003	LE, F		Intra-NAC 6-OHDA in SR & IR rats	blocked ↓ in PPI in IR rats
Schwienbacher et al. 2002	SD, M	+ VTA	Infusion of DAergic, adenosinergic, or GABAergic compounds into NAC and/or VTA	↑ PPI after combined VTA PTX + NAC SCH23390
Swerdlow et al. 2006d	SD, LE and F1 (SDxLE), M	+ Striatum	Measured DA-stimulated [^{35}S]GTPγS-binding in NAC, striatum	PPI-APO sensitivity: SD>F1>LE. [^{35}S]GTPγS-binding in NAC, striatum: LE>F1>SD
		II. HPC		
			Adults	
Ellenbroek et al. 2002b	WI, M	CA1	Infusion of AMP, SKF81297 or QUIN	↓ PPI after AMP, SKF81297 or QUIN; AMP-induced PPI deficits blocked by intra-NAC SCH23390 but not sulpiride
Ma and Leung 2004	LE, M	CA1	Electrical kindling	↓ PPI (and ↓ PA)
Finamore et al. 2001	Rats		Infusion of KA or NMDA antagonists	↓ PPI with infusion of NMDA antagonists
Fitting et al. 2006a	SD, M		Infusion of viral toxin TAT	↑ PPI (and ↓ PA)
Inada et al. 2003	WI, M		Antisense NR1 knockdown	↓ PPI with knockdown 6, but not 14d pre-testing

Table 4 (continued)

Reference	Rat strain, sex	Brain regions	Manipulation	Effect on PPI
			Neonates	
Fitting et al. 2006c	SD, M, F		Neonatal infusion of viral toxin gp120	↓ PPI (and ↑ PA); + Vehicle: ↓ PPI with increasing gp120 doses. + APO: ↑ PPI with increasing gp120 doses
Fitting et al. 2006b	SD, M, F		Neonatal TAT infusion	Males: ↓ PPI at d 30 and 60, but not d 90
		vHPC		
			Adults	
Howland et al. 2004b	LE, M	+ dHPC	Electrical stimulation VHPC vs. DHPC combined with NAC microdialysis	↓ PPI after VHPC but not DHPC stim.; ↑DA efflux: ipsi- but not contralateral NAC after unilateral stim. VHPC but not DHPC
Klamer et al. 2005b	SD, M		Microdialysis of the VHPC after systemic (or local) PCP	↓ PPI and ↑ cAMP after PCP; blocked by NO-synthase inhibitor L-NAME
Kusljic and van den Buuse 2004	SD, M	+ dHPC	5,7-DHT lesion	↓ PPI for DHPC lesioned rats, and partially for VHPC lesioned rats
Zhang et al. 2002a	WI, M	+ dHPC	Infusion of NMDA	↓ PPI after intra-VHPC but not -DHPC infusion
Swerdlow et al. 2004b	SD, M	+ FX	Infusion of NMDA into the VHPC in rats with EL lesions of the FX	↓ PPI after NMDA infusion into VHPC, unaffected by FX lesion; IA lesion of the VHPC but not EL FX lesion enhanced ↓PPI by APO
			Neonates	
Laplante et al. 2005	SD, M		IA-neonatal lesion	↓ PPI; blocked by biperiden
Zhang et al. 2002b	WI, M	+ dHPC	Muscimol or TTX infusion	↓ PPI, not blocked by HAL or CLO
Risterucci et al. 2005	SD, M		IA-neonatal lesion	↓ PPI, ↓ blood flow in NAC, BLA,VP, BNST, entorhinal–piriform and orbital CTX
			Adults	
Caine et al. 2001	LH, M	**dSUB or vSUB**	QA-lesions	↓ PPI after vSUB lesions. ↓ PPI to AMP (not APO) after vSUB lesions.
		III. PFC		
			Adults	
de Jong and van den Buuse 2006	SD, M		Infusion of SCH23390	enhanced PPI deficits to APO but not DIZ
			Neonates	
Grobin et al. 2006	M, F	+ MD	Neonatal elevation of allopregnanolone	↓ PPI in castrates before and after puberty (PD20 and 80), but ∅ PPI during puberty (PD40 and 60)
Rajakumar et al. 2004	SD, M		Neonatal infusion of antibody to the p75 neurtrophin receptor	↓ PPI at age 10 wks, but not 5 wks

		mPFC		
			Adults	
Afonso et al. 2007	SD, F		NMDA-lesion	↓ PPI
Bast et al. 2001	WI, M		Infusion of NMDA	↓ PPI, not blocked by HAL or CLO
Day-Wilson et al. 2006	LH, M		IR (associated with ↓mPFC volume)	↓ PPI
Schwabe and Koch 2004	WI, M		IA-lesion	lesion blocked DIZ-induced ↓ PPI but not APO-induced ↓ PPI
Shoemaker et al. 2005	SD, M		Infusion of SCH23390 into the mPFC; infusion of NMDA into the VHPC in rats with IA mPFC lesion	↓ PPI after infusion of SCH23390 in mPFC; mPFC lesions block ↓ PPI after intra-VHPC NMDA infusion
Swerdlow et al. 2006c	SD, M	+ NAC	Systemic SCH23390, IA lesion of mPFC, 6-OHDA DA depletion of mPFC or NAC	↓ PPI after SCH23390, not blocked by either NAC DA depletion or mPFC lesion; ↓ PPI after mPFC DA depletion
			Neonates	
Schneider and Koch 2005	WI, M		IA-neonatal lesion	↑ PPI in juveniles; enhanced PPI deficits to APO in adults
Schwabe et al. 2004	WI, M		IA-neonatal lesion	↑ PPI after neonatal lesions; ↓ PPI in both lesioned and intact rats after APO
		IV. eCTX		
			Adults	
Goto et al. 2002	WI, M		IA lesion	↓ PPI, partially blocked by HAL
Goto et al. 2004	WI, M	+ NAC	eCTX lesion with IA, microdialysis of NAC	↓ PPI, ↑ DA concentration in NAC
Uehara et al. 2007	WI, M	+ mPFC	eCTX lesion with QA, mPFC lidocaine infusion	↓ PPI after eCTX lesion or mPFC lidocaine
		V. AMY		
			Neonatal	
Daenen et al. 2003	F1 of WI/UWU, M	**AMY (or vHPC)**	Neonatal AMY or VHPC lesions with IA	↓ PPI in rats lesioned in the AMY or VHPC on d 7, but not on d 21
		BLA		
			Adults	
Howland et al. 2007	LE, M	+ eCTX, + vHPC	Electrical kindling	↓ PPI shortly after kindling of BLA, but not of eCTX or VHPC
Kusljic and van den Buuse 2006	SD, M	+ CnA	5,7-DHT lesion	↓ PPI with lesions of CnA but not BLA
Shoemaker et al. 2003	SD, M		QA lesion of the BLA	↓ PPI, blocked by quetiapine
Stevenson and Gratton 2004	LE, M	+ Striatum	Infusion of SCH23390 or raclopride	↑ PPI after intra-BLA SCH23390, ↓ PPI after intra-BLA raclopride

Table 4 (continued)

Reference	Rat strain, sex	Brain regions	Manipulation	Effect on PPI
		VI. MD		
			Adults	
Swerdlow et al. 2002c	SD, M		Infusion of QUIN or TTX	↓ PPI after TTX but not QUIN, not blocked by quetiapine
		VII. Habenula		
			Adults	
Heldt and Ressler 2006	Mice, C57, M		Electrolytic lesion	∅ PPI in the absence of stress; but ↓ PPI after stress in habenula lesioned rats; blocked by CLO
		VIII. mS		
			Adults	
Ma and Leung 2007	LE, M	+ SUM	Infusion of muscimol	Muscimol into mS or SUM blocked ketamine- or DIZ-induced PPI deficits
Ma et al. 2004	LE, M		Infusion of muscimol	Infusion of muscimol into mS blocked PCP-induced PPI deficits
		IX. NBM		
Ballmaier et al. 2002	SD, M		Immunolesion of cholinergic NBM neurons	↓ PPI, blocked by single or repeated admin. of rivastigmine
		X. IC		
			Adults	
Silva et al. 2005	LE, M		Electrical stimulation	↓ PPI
Sandner et al. 2002	SD, M	+ PnC	Evoked potentials from IC or PnC	↓ PPI by ketamine and ↑ evoked potentials
Yeomans et al. 2006	WI, M	SC, + intercollicular nuc. or PPTg	Electrical PP and pulses via electrodes to the SC, IC, intercollicular nucleus, or PPTg	PPI after electrical PP to most SC sites. Longer PPI latencies for electrical PP to the SC than IC, intercollicular nuc. or PPTg
		XI. PPTg		
			Adults	
Diederich and Koch 2005	WI, M		Infusion of muscimol	↓ PPI at intervals≥120 ms
Takahashi et al. 2007	Mice, ICR, M	+ lGP, ssCTX	Infusion of phaclofen into the PPTg or lidocain into the lGP, c-fos labeling of brain regions after acoustic pulses or prepulses	↓ PPI after intra-PPTg phaclofen or intra-lGP lidocaine; ↑c-fos in lGP after prepulses; ↑c-fos in NAC shell, PnC, and ssCTX after pulses, blocked in NAC and PnC by prepulses
		XII. LDTN, SN		
			Adults	
Jones and Shannon 2004	SD, M		IA-lesion of the LDTN or SN	↓ PPI after lesion of LDTN but not SN

Table 4 (continued)

Reference	Rat strain, sex	Brain regions	Manipulation	Effect on PPI
		XIII. DRN or MRN		
			Adults	
Kusljic et al. 2006	SD, M		5,7-DHT lesion	↓ PPI in MRN but not DRN lesioned rats, blocked by HAL or CLO
Kusljic et al. 2003	SD, M		5,7-DHT lesion	↓ PPI at all PP intensities for MRN-lesioned rats and for some PP intensities for DRN lesioned rats
		XIV. Brainstem		
			Neonates	
Shishkina et al. 2004	WI, M		Neonatal infusion of antisense oligonucleotide complementary to the α2 adrenoceptor	↓ PPI at PD34, associated with ↑α2 adrenoceptors in HPC, AMY

AMP Amphetamine, *AMY* amygdala, *APO* apomorphine, *BG* background, *BLA* basolateral amygdala, *BNST* bed nucleus of the stria terminalis, *C57* C57BL/6J, *CLO* clozapine, *CnA* central nucleus of the amygdala, *CPA* N(6)-cyclopentanyladenosine, *CTX* cortex, *d* dorsal, *5,7-DHT* 5,7 dihydroxytryptamine, *DIH* dihydrexidine, *DIZ* dizocilpine, *DRN* dorsal raphe nucleus, *e* entorhinal, *EL* electrolytic, *F* females, *FX* fornix, *HAL* haloperdidol, *HPC* hippocampus, *IA* ibotenic acid, *IC* inferior colliculus, *IR* isolation rearing, *KA* kainic acid, *l* lateral, *LDTN* laterodorsal tegmental nucleus, *LE* Long Evans, *LH* Lister Hooded, *M* males, *m* medial, *MD* dorsomedial thalamus, *MET* methamphetamine, *MRN* median raphe nucleus, *NAC* nucleus accumbens, *NBM* nucleus basalis of Meynert, *NMDA* *N*-methyl-D-aspartate, *NO* nitric oxide, *OVX* ovariectomized, *NT* neurotensin, *6-OHDA* 6-hydroxydopamine, *PD* postnatal day, *PA* pulse alone trial, *PCP* phencyclidine, *PFC* prefrontal cortex, *PnC* nucleus reticularis pontis caudalis, *PPI* prepulse inhibition, *PPTg* pendunculopontine nucleus, *PTX* pertussis toxin, *QA* quinolinic acid, *QUIN* quinpirole, *S* septum, *SD* Sprague–Dawley, *SC* superior colliculus, *SN* substantia nigra, *Sp-cAMP* cyclic adenosine monophosphate analogue, *SR* socially reared, *ss* somatosensory, *SUB* subiculum, *SUM* supramamillary area, *v* ventral, *VP* ventral pallidum, *VTA* ventral tegmental area, *WI* Wistar, ↓ decreased, ↑ increased, ∅ unchanged positive or negative symptoms scores (Table 1). Certainly, there is much interest in determining whether, with repeated or longitudinal measures, a change in PPI predicts or accompanies clinical deterioration or improvement, including the prediction of illness onset in prodromal subjects (Cadenhead 2002; Addington et al. 2007; Cannon et al. 2008). Very few studies have collected longitudinal measures of PPI in schizophrenia populations with adequate sample size and duration to be informative, although some are in progress. One might predict a relationship between PPI and psychosis in extreme conditions, such as the shift from euthymic to manic bipolar disorder, but even in this case, studies have been limited to cross-sectional comparisons, and results across studies have not been consistent (Perry et al. 2001; Rich et al. 2005; Barrett et al. 2005; Carroll et al. 2007). Duncan et al. (2006a, b) did detect an association between lower levels of PPI, and greater levels of psychotic symptoms and psychological discomfort among unmedicated schizophrenia patients.

Interestingly, while robust relationships between PPI and the most common clinical indices of schizophrenia have been hard to detect, reports have identified significant correlations between PPI and a number of relatively complex clinical measures, ranging from quantitative Rorschach ink blot indices of thought disturbance (Perry and Braff 1994) to scales of distractibility and attention (Karper et al. 1996). One report (Swerdlow et al. 2006f) identified a significant positive correlation between PPI and global functioning levels (GAF score) in schizophrenia patients, but this relationship was evident only among male patients, and the correlation—while highly significant ($p<0.005$)—accounted for a relatively modest amount of the total PPI variance. In addition, PPI levels were associated with levels of independent living, also perhaps reflecting its relationship to global functioning. As a result, more sophisticated and sensitive analyses of PPI, related gating measures, and function in schizophrenia patients are being pursued (Light et al. 2007a; Braff et al. 2007a). Studies have detected modest but statistically significant relationships between PPI and measures of executive function in some patient groups [e.g., children with 22q11DS (Sobin et al. 2005a, b)]. A preliminary qualitative article by Butler et al. (1991) noted a nonsignificant trend toward greater tactile (but not acoustic) PPI among six (predominantly male) patients with schizophrenia and low levels of Wisconsin Card Sorting Test perseverative responses than among nine (predominantly female) patients distinguished by high levels of Wisconsin Card Sorting Test (WCST) perseverative responses. Kumari et al. (2007a) recently reported a significant ($p<0.03$) correlation between tactile PPI and WCST perseverative responses in male schizophrenia patients. Significant positive relationships between acoustic PPI and working memory as well as other formal indices of neurocognitive function have been detected among clinically normal individuals (Bitsios et al. 2006; Light et al. 2007b, 2008; Csomor et al. 2008), although no such relationships have been reported for schizophrenia patients.

The relative insensitivity of PPI to clinical *state* speaks of the importance of *trait* features of this measure, which may reflect more "hard-wired" anatomical and genetic determinants. The fact that some relationships can be detected between PPI and relatively global measures of function in schizophrenia patients, but not between PPI and clinical state per se, is consistent with the hypothesis that the causal link between genes and functional outcome in schizophrenia reflects the impact of forebrain circuits that regulate basic gating mechanisms, more than those that control the expression of specific symptom states (Light et al. 2004; Braff and Light 2004; Light and Braff 2005). Thus, while diagnosis in schizophrenia will remain symptom-based for the foreseeable future, it could be argued that studies of the biology of schizophrenia and its relationship to functional outcome may be best advanced through quantitative measures of forebrain inhibitory function such as PPI.

Treatment

As PPI deficits in schizophrenia reflect dysfunction in forebrain circuitry and are linked to both cognitive and functional deficits in schizophrenia patients, can PPI or its potentiation by drugs in patients be used to predict individualized treatment for this disorder? Certainly, in terms of preclinical predictive models, PPI has been quite powerful, as discussed below. In schizophrenia patients, cross-sectional data and some longitudinal findings demonstrate that antipsychotic treatment is associated with elevated (i.e., "normalized") PPI and that this association is most robust with atypical antipsychotics as a class, compared to first generation antipsychotics (Table 1). Of course, interpreting medication effects in most of these reports is difficult because patients are uniformly being treated with complex multidrug regimens across a range of doses, and medication compliance is known to be poor among schizophrenia outpatients (Lieberman et al. 2005). A recent controlled study with a multidrug cross-over design detected PPI-increasing effects of olanzapine (but not risperidone or haloperidol) in chronically ill schizophrenia patients (Wynn et al. 2007). Findings of PPI-increasing effects of both quetiapine and clozapine in clinically normal, "low-gating" subjects suggests that the PPI-increasing effects of these drugs in schizophrenia patients may not reflect disorder-specific processes (Swerdlow et al. 2006a; Vollenweider et al. 2006). We do not know if the PPI-enhancing effects of these drugs, and conceivably some of their clinical benefit, may reflect their ability to optimize function within spared (intact) gating mechanisms, rather than their ability to correct or normalize activity within dysfunctional mechanisms.

Still, it is reasonable to ask whether the ability of drugs to normalize PPI in patients, or to increase PPI in "low-gating" normals, might reflect their impact on brain processes and resulting cognitive abilities that ultimately would have clinical utility and perhaps cognitive-enhancing effects in schizophrenia. While clinically effective antipsychotics (particularly atypical antipsychotics) are associated with increased PPI in patients and low-gating normals (Table 1), PPI is also increased in non-patients by ketamine and methylenedioxymethamphetamine (MDMA; discussed below; Duncan et al. 2001; Abel et al. 2003; Vollenweider et al. 1999), neither of which would be on anyone's list of likely antipsychotic agents. Nicotine is associated with increased PPI in schizophrenia patients (Kumari et al. 2001; Swerdlow et al. 2006f), but despite the hypothesis that smoking reflects a form of "self-medication" in schizophrenia patients, there is no clear evidence for either antipsychotic or cognitive-enhancing effects of nicotine in these patients. While there is an active quest by many groups to develop cognitively enhancing nicotinic receptor-specific agonists, based on the putative relationship between the alpha-7 nicotinic receptor subtype and schizophrenia (Freedman et al. 1997), there is presently no evidence that such compounds either increase PPI or enhance cognition in patients. Thus, screening compounds as effective antipsychotics based on their PPI-enhancing effects in clinical or special populations is likely to yield both true and false positives. At this point, there is an inferential, but not empirical, basis for using PPI enhancement as a basis for predicting the ability of a compound to enhance cognition and real-world daily functioning in schizophrenia. Clearly, this is an area of active investigation, and such empirical evidence might emerge based on these efforts.

A reliable, robust quantitative phenotype

While the realistic expectations for PPI as a clinically useful biomarker may be somewhat limited, it is very realistic to expect that PPI will continue to be a valuable tool for investigating brain functions relevant to several neuropsychiatric disorders, including schizophrenia. The many strengths of PPI as an experimental measure have been reviewed elsewhere (Braff et al. 2001b), and none of the realistic limitations described above detract from its attributes as an objective, quantifiable, reliable, robust, neurochemically and parametrically sensitive cross-species measure of a neurobiologically important process. Nonetheless, even in its use as an investigative experimental tool in humans, there should be a realistic assessment of what we can and cannot expect from PPI.

Two types of studies speak strongly to the general reliability of this quantitative phenotype. First, test–retest reliability has been established for PPI in normal comparison subjects (NCS), across days (Abel et al. 1998; Swerdlow et al. 2001c; Flaten 2002), weeks, and months (Cadenhead et al. 1999; Ludewig et al. 2002). More recently, 1-year retest data collected in 68 schizophrenia patients yielded intra-class correlations of 0.75 (30 ms)–0.89 (120 ms; Light et al. 2007a), suggesting a very high stability of this phenotype in patients. Second, a multisite study of PPI in NCS was conducted, using carefully standardized equipment, test methods, and inclusion/exclusion criteria. No significant differences in PPI were detected across seven geographically dispersed test sites, despite some modest methodological drift that was detected via rigorous quality assurance efforts (Swerdlow et al. 2007). Thus, within individuals, and across test samples, PPI appears to be a reliable phenotype.

While PPI is a reliable phenotype, at least among NCS, it is not reasonable to expect that every schizophrenia patient will exhibit a "deficient-PPI" phenotype. In fact, as noted above, there is no way to test this possibility because there is no absolute value that defines "deficient" PPI. Under commonly used test conditions, there is substantial overlap in the distribution of PPI values, between schizophrenia patients and community comparison subjects (cf. Braff et al. 2001b). Clearly, there are schizophrenia patients who have higher levels of PPI compared to many NCS. The overlapping group distributions with this measure likely reflect the many influences on PPI, other than schizophrenia-related pathology, such as sex, hormonal status, smoking, withdrawal from caffeine or nicotine, fatigue, and medications. There are also normal interindividual differences in activity within brain circuitry (e.g., in the pallidum, pons, or cerebellum) that regulates PPI, but is not primarily involved in schizophrenia. With typical testing parameters, NCS vs. unmedicated patients or patients receiving only typical antipsychotics, group separation in mean percent PPI might be reasonably expected to reach 1 SD (e.g., Kumari et al. 1999; Ludewig et al. 2003; Swerdlow et al. 2006f), which corresponds to 55% non-overlap. However, when patients taking atypical antipsychotics are included, group separation drops dramatically, to about 0.3 SD (e.g. Swerdlow et al. 2006f)—or 21% nonoverlap. This latter fact is particularly important, given that upwards of 90% of schizophrenia patients in most current open-enrollment studies report taking atypical antipsychotic medications [although true compliance is likely lower (Dolder et al. 2002; Lacro et al. 2002)].

In addition to medication status, studies have reported many other variables in patient selection that influence group separation in comparisons of schizophrenia patients vs. NCS. One issue that may ultimately impact the utility of

PPI as a quantitative phenotype is its potential sensitivity to ascertainment bias. As noted above, PPI correlates positively with global function in schizophrenia patients. Thus, on average, studies of lower functioning patients will detect greater separation vs. NCS, and those of higher functioning patients will detect less group separation. For this reason, investigators are considering the impact of study designs that select for higher- vs. lower-functioning schizophrenia patients, such as those that require a proband within an intact family structure (and who thus may be relatively higher functioning) vs. those utilizing patients without intact families, who are often homeless or medically indigent (Calkins et al. 2007).

Perhaps equally important as the selection of patients is the selection of NCS. Comparison samples differ substantially across studies and can range from generally healthy, young college students, to "professional controls", who are often low-functioning and unemployed, beyond their activities as test subjects in biomedical research. The latter group is more likely to have histories of disorders that are associated with reduced PPI, such as anxiety disorders (OCD, panic disorder or post-traumatic stress disorder) or "cluster A" personality disorders; they may also be more likely to carry vulnerability genes for neuropsychiatric disorders, take psychotropic medications that influence PPI, and have histories of substance use or brain trauma that might impact PPI-regulatory brain circuitry. Much has been written about the considerations in selecting a "matched", "representative", "normal" or "supernormal" comparison group in biomedical research (e.g., Roy et al. 1997; Calkins et al. 2004), and without belaboring this point, these same considerations apply to studies of PPI and may greatly impact group separation in comparisons of control vs. schizophrenia populations.

As reviewed in Braff et al. (2001b) and elsewhere, the amount of separation between schizophrenia and NCS populations in PPI is highly dependent on testing conditions, and specifically, on stimulus parameters. Thus, if all else is equal, schizophrenia-linked PPI deficits are most pronounced under conditions in which prepulse salience, often based on its intensity over background, is within a "dynamic range": not too high, but not too low. For example, most studies find this "sweet spot" of maximal schizophrenia vs. NCS separation using discrete white noise prepulses 8–16 dB over a 70-dB(A) background, with about 60 ms prepulse intervals [or stimulus onset asynchronies (SOAs; Table 1)]. Some studies failing to detect PPI deficits in schizophrenia samples have used prepulses in the absence of a background white noise, effectively creating very large prepulse intensities of 25–40 dB(A; Hazlett et al. 2003, Wynn et al. 2004, 2005). In addition to prepulse intensity relative to background, prepulse frequency (e.g., tone vs. white noise), duration (discrete vs. continuous) and other variables (including the use of binaural vs. mono-aural stimuli) may contribute to maximizing the group separation in PPI between schizophrenia and NCS populations (Braff et al. 2001a; Hsieh et al. 2006; Kumari et al. 2005b, 2007b).

As noted above, the temporal "sweet spot" for detecting automatic (uninstructed) PPI deficits in schizophrenia patients appears to occur with prepulse intervals between 30 and 240 ms, depending somewhat on other stimulus characteristics. The temporal range around 60 ms appears to be most sensitive in several studies (Braff et al. 1978, 1992, 2005; Weike et al. 2000; Leumann et al. 2002; Swerdlow et al. 2006f) and may be the range in which PPI deficits are most resistant to normalization by antipsychotic medications. Interestingly, this interval sits at the juncture between preconscious and conscious information processing, based on perceptual detection thresholds (Libet et al. 1979; Kanabus et al. 2002). The possibility that PPI in this temporal range may be most deficient in schizophrenia suggests that automatic inhibitory mechanisms may be most "porous" at a critical barrier between preconscious processing and conscious awareness. While clearly a point for more systematic analysis, such a notion suggests a biological mechanism that is syntonic with psychological models for the intrusion of unedited, preconscious content into conscious awareness in this disorder (Libet et al. 1979; Gray 1995; Swerdlow 1996; Grobstein 2005).

A useful tool for probing the neurobiology and genetics of gating deficits in schizophrenia

Perhaps the most realistic expectation is that PPI is and will remain a useful tool for studying the neurobiology of information processing abnormalities in schizophrenia. While the PPI deficit "signal" in genetic studies of schizophrenia has been blunted by the widespread use of atypical antipsychotics, investigators are increasingly well informed about the many other factors affecting the measurement of PPI and the detection of schizophrenia-associated deficits, and in this way are better positioned to study the basis for these deficits at the levels of their neurobiological and genetic substrates. These studies will be aided by special populations, including "low-gating" normals (Swerdlow et al. 2006a; Vollenweider et al. 2006) and asymptomatic relatives of schizophrenia probands (Kumari et al. 2005b), and by patients with related disorders, such as 22q11 deletion syndrome and unmedicated "prodromal" individuals (Sobin et al. 2005a, b).

As a relatively robust and reliable quantitative phenotype, PPI will be used to map genes associated with deficient sensorimotor gating in schizophrenia probands and families (Swerdlow et al. 2007; Greenwood et al. 2007). The strength of this "endophenotype" approach to understanding disease genetics has been described by many, including Gottesman and Gould (2003), Gould and Gottesman (2006), and Braff et al. (2007a), and largely reflects the fact that the quantitative laboratory measure (in this case, PPI), is closer to the underlying biology (i.e., aberrant neural circuits and their regulation by disease genes), compared to the more variable clinical phenotype (Braff et al. 2007a). There are a small but growing number of examples in which this strategy has proven successful, in identifying genes that confer risk for colon cancer (Leppert et al. 1990) and Type II diabetes (Scott et al. 2007). Whether this strategy can succeed in identifying vulnerability genes for more complex neuropsychiatric disorders is a question at the core of several large ongoing investigative efforts.

Gains will likely be made through the combined use of PPI with sophisticated neurocognitive, neuroimaging, and genetic/genomic tools in schizophrenia and normal populations. It is realistic to expect that these various applications will converge in a top down or bottom up fashion, i.e., to link: (1) genes with (2) brain substrates that cause (3) gating deficits responsible for (4) neurocognitive disturbances and (5) the resulting daily functional impairment in schizophrenia. Based on the genes and brain substrates identified in these studies, one might reasonably expect that novel treatments will be identified, perhaps acting on intracellular G-protein-coupled signal transduction mechanisms that have already been implicated in the regulation of PPI (van den Buuse et al. 2005a; Kelly et al. 2007; Swerdlow et al. 2006d; Culm et al. 2004; Svenningsson et al. 2003), and which may also be abnormal in some schizophrenia patients (cf. Catapano and Manji 2007). There are also mature lines of research suggesting that novel treatments may target neuropeptides, such as neurotensin (Kinkead et al. 2005; Feifel et al. 2004), that potently regulate PPI and its dopaminergic control, or may target specific dopamine receptors subtypes that regulate PPI via relatively localized effects within mesolimbic and limbic–fronto–striatal circuits (e.g., Zhang et al. 2006). At some stage, it is reasonable to expect that the development of any one of these or other novel treatments might be guided by their effects on PPI in control or clinical populations.

A surrogate measure for neural processes with wide-reaching psychological implications

The frontal, limbic, and mesolimbic circuitry that regulates PPI also regulates many higher-order psychological processes. Thus, PPI can be viewed as a simple surrogate "readout" of activity in this circuitry—an experimentally generated signal from the forebrain, detected through efferents descending through a "pontine portal". Alternatively, PPI can be viewed as a measure of a fundamental psychological process—sensorimotor gating—with broad-reaching implications for the structure of complex behavior and thoughts. In truth, both views are at least partly accurate, under specific uses of the PPI paradigm.

"Gating" can be a very specific process when operationalized in the laboratory, but is less precisely defined when used as a psychological construct. How broadly can we extrapolate from the laboratory measure of one type of gating—sensorimotor gating—to other forms of automatic inhibition of sensory, cognitive, or motor information? There is credible evidence that PPI correlates significantly with a form of perceptual "gating", measured by the degree to which the prepulse reduces the perceived intensity of the startling stimulus (Peak 1939; Swerdlow et al. 2005b). On the other hand, PPI does not correlate strongly with the most structurally similar form of "gating"—sensory gating—measured by suppression of the P50 auditory event-related potential (ERP; Light et al. 2006; Hong et al. 2007). Nor does PPI in normal humans correlate strongly with other measures thought to assess inhibitory processes that contribute to forms of "cognitive gating", such as latent inhibition (Murphy et al. 2001; Leumann et al. 2002; Peleg-Raibstein et al. 2006a, b) or visuospatial or semantic priming (Swerdlow et al. 1995b). Certainly, there is little evidence that PPI assesses processes that are strong determinants of normal personality structure and dimensions (Swerdlow et al. 2003d). At the least, it is important to recognize that the construct of "gating" is applied to many different processes and that it is reasonable to expect PPI to be informative about some, but not all or even most of these processes.

Summary: human studies

Human studies of PPI will continue to provide one important level of information within a top down or bottom up understanding of the biology of schizophrenia. PPI offers great promise as a quantitative phenotype for genetic studies and will be used in combination with other measures to connect an aberrant physiological signal (impaired startle inhibition) with its underlying neural substrates (via neuroimaging studies) and with its consequences in terms of cognitive deficits (via neurocognitive measures) and real-life impairment (via functional measures). It is realistic to expect that as we gain a better understanding of its modulating variables and optimal experimental methods, PPI in humans will continue its evolution, started in 1978 (Braff et al. 1978) from an isolated laboratory-based psychophysiological phenomenon, into a productive clinical research tool for understanding psychopathology. As we learn more about PPI, our scientific approaches to its use will continue to become more sophisticated, and we will be better positioned to take full advantage of what it can tell us about normal and abnormal brain functions.

Animal studies: What can our field realistically expect to learn about schizophrenia based on studies of PPI in laboratory animals?

Etiology

Two general applications of animal studies of PPI will be considered here: (1) the use of PPI to evaluate models or model organisms relevant to the etiology of schizophrenia; and (2) the use of PPI to "map" the neural substrates of deficient PPI in schizophrenia.

Model organisms, created via genetic, developmental, surgical, pharmacological, or immune manipulations, have been a mainstay of studies of the etiology, pathophysiology, and treatment of schizophrenia. Of course, schizophrenia—as defined clinically—is a uniquely human disorder (least we ascribe to rats the ability to have "two or more voices conversing with one another or voices maintaining a running commentary on the [rat's] thoughts or behavior," or the ability to conceptualize that "alien thoughts have been put into his or her mind...", or to have homologous complex social cognitive deficits; APA 2000). However, investigators can apply schizophrenia-linked constructs to these models and test whether the resulting animal reproduces laboratory-based phenotypes exhibited by schizophrenia patients. The degree to which these phenotypes are reproduced in the model organism provides a level of validity to the construct, even if it is specific to the laboratory-based phenotype, rather than the broader clinical disorder.

For example, given a particular schizophrenia candidate gene "*X*", it is reasonable to ask whether manipulations of gene "*X*" produce an animal that exhibits reduced levels of PPI compared to a wild-type animal. If so, then the gene "*X*" mutant would be a valid model for *PPI deficits in schizophrenia*. Such an approach has been taken with many different animal models (Table 3). There are obvious limitations to the specificity and sensitivity of this approach, which could be deduced from the above discussions of the PPI findings in humans.

Because deficient PPI is not unique to schizophrenia populations, there is no a priori justification for claiming that such a mutant specifically models the PPI deficits in schizophrenia, rather than OCD (Swerdlow et al. 1993a; Hoenig et al. 2005), Tourette Syndrome (Smith and Lees 1989; Castellanos et al. 1996; Swerdlow et al. 2001b), Blepharospasm (Gomez-Wong et al. 1998), or a number of other conditions. The specificity of the linkage of the model with schizophrenia, and hence with PPI deficits in schizophrenia, must come from the construct. For example, the finding of PPI deficits in a murine model of 22q11 deletion syndrome (22q11DS) links this model to PPI deficits in schizophrenia (Paylor et al. 2006; Sobin et al. 2005a, b), on the basis of the clinical relationship between 22q11DS and schizophrenia. Without this clinical relationship, this would just be a mouse with low PPI, and the model would most likely be a "false positive" for the schizophrenia phenotype.

Certainly, it is unlikely that most genes associated with low vs. high levels of PPI will be related to reduced PPI in schizophrenia or any one other disease states. This is because the most potent influences regulating baseline PPI involve physiological substrates that are probably *not* relevant to schizophrenia. For example, a very potent determinant of acoustic PPI is *hearing threshold*, as an organism that cannot hear a prepulse will not exhibit PPI. Thus, many candidate "PPI genes" identified via gene inactivation or mapping strategies of drug-free PPI in inbred and recombinant rodents will likely be associated with hearing threshold. Beyond the level of sensory detection, the most potent neural control of baseline PPI is exerted by the pedunculopontine nucleus (PPTg) (Swerdlow and Geyer 1993a), which mediates PPI via its impact on the nucleus reticularis pontis caudalis (NRPC; Koch et al. 1993). For the same reasons noted for hearing threshold, genetic studies of PPI will likely be influenced strongly by genes coding for the normal function of the PPTg—a structure that does not play a central role in any model for the pathophysiology of schizophrenia. In contrast, the prefrontal cortex (PFC)—which is viewed as a critical substrate for some core symptoms of schizophrenia (e.g., cognitive disorganization, deficient working memory, executive functioning, abstract reasoning, cognitive flexibility and context processing, and negative symptoms)—is likely to be three or four synapses removed from the primary startle circuit; in a normal human or rodent, genes controlling the PFC will likely contribute only weakly to a genetic "signal" based on levels of baseline PPI.

One might argue that a finding of PPI deficits provides additional validation that a particular model reproduces one of the quantitative phenotypes associated with schizophrenia. But as noted above, there is no definitive evidence that PPI deficits—or the neural abnormalities that produce them—are *necessary* for the expression of the broader schizophrenia phenotype. Rather, it is almost certainly true that there are large numbers of functionally impaired, symptomatic schizophrenia patients who exhibit levels of PPI in the "normal" range. Thus, rejecting animal models on the basis of "normal" PPI levels would likely result in a number of "false-negative" models—i.e., ones in which some features of the model accurately recreate important aspects of the biology of schizophrenia, but do not result in reduced PPI.

Perhaps the most realistic expectation of PPI in the assessment of animal models of schizophrenia is that it can provide validation for specific existing constructs—i.e., that the construct can reproduce PPI deficits exhibited by a significant subgroup of the heterogeneous population of schizophrenia patients. On the other hand, "normal" or unaltered PPI should not be used as the basis for rejecting a model: even in the presence of "normal" (i.e., wild-type, sham lesioned or placebo-treated) PPI levels, it is very possible that a model might be highly informative about the biology of schizophrenia.

Animal studies are also used to explicate the neural regulation of PPI, as a means of understanding the neural basis of PPI deficits in schizophrenia and other disorders. In this case, the manipulations are selected not necessarily based on a "construct" of schizophrenia, but rather based on the extant PPI neural "map", and the understanding of anatomical and neurochemical properties of that map. In general, the organism used in these studies is not a schizophrenia "model" per se, but is more akin to a canvas on which a neural map can be painted. A reasonably comprehensive understanding of this "map", ca. 2000, is found in Swerdlow et al. (2001a), and an updated list of studies of "PPI anatomy" is found in Table 4.

Much can be gleaned about PPI and its broader context by considering two facts related to its anatomical substrates.

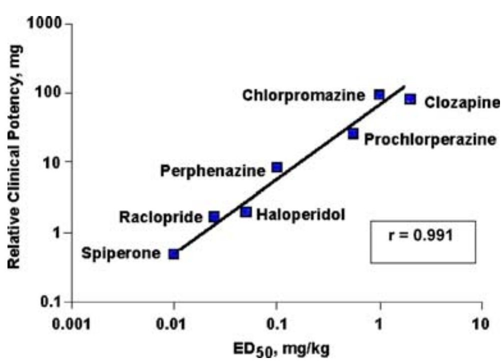

Fig. 2 Evidence supporting the predictive validity of one "rapid-throughput" animal model of PPI deficits. In these studies (Swerdlow et al. 1994), PPI was disrupted in adult male Sprague–Dawley rats by the mixed D1/D2 agonist, apomorphine (0.5 mg/kg sc). The ED50 of a number of drugs to reverse this apomorphine effect correlated significantly with their clinical potency. Subsequent studies have identified many other clinically effective antipsychotic agents from different chemical classes that prevent the PPI-disruptive effects of apomorphine in rats [see Table 2 and Geyer et al. (2001)]. A small number of potential "false-positive" compounds have also been detected, primarily in other species or strains. Other predictive models have been developed using PPI as a dependent measure, as described in the text and Table 2, each with different sensitivity, specificity, and logistical complexities

First, PPI remains intact after acute trans-collicular decerebration in the rat (Davis et al. 1982). In other words, the expression of unimodal acoustic PPI in rats does not *require* any part of the forebrain, and therefore, it must be *mediated* at or below the pons. The prepulse does not (and by physical and temporal constraints, *cannot*) "travel" to the forebrain to generate its inhibitory impact on the simple startle reflex (see discussion in Swerdlow et al. 2001a). *Second*, PPI can be *regulated*, and even eliminated, by subtle pharmacological manipulations at the most rostral tip of the forebrain [e.g., D1 receptor blockade within the medial prefrontal cortex (Ellenbroek et al. 1996; Shoemaker et al. 2005; Swerdlow et al. 2005c)]. Thus, brain substrates at the furthest point from the PPI "mediating" circuitry in the pons are capable of potently regulating the amount of inhibition generated by the prepulse, presumably via *tonic*, "*thermostat*"-*like* stimulus-independent changes in activity within descending circuitry.

These two facts lead to a simple conclusion: while PPI *is mediated via* the pons, it can be *regulated* by the forebrain. A relative loss of PPI in clinical populations, and in the animal models that are used to study them, can be a consequence of aberrant activity within this descending circuitry—somewhere "between" the cortex and pons—or within substrates that impinge upon it. The efforts to "map" this PPI-regulatory circuitry, point-to-point, from cortex to pons, are aimed to help investigators identify candidate substrates that contribute to the loss of PPI in patient populations and candidate targets for therapeutic interventions. Of the many words of caution related to this use of animals to "map PPI", two will be noted here.

First, rodent brains and human brains are not the same. Thus, a map of neural circuitry regulating PPI in rodents cannot be expected to translate exactly to human brains. Indeed, it is surprising how much overlap is suggested across species, based on neuroimaging findings in humans (Kumari et al. 2003a, 2005, 2007a; Postma et al. 2006), and based on examples of localized neuropathology associated with PPI deficits in brain disorders such as HD and in rat and murine models of this disorder (Swerdlow et al. 1995a; Carter et al. 1999; Van Raamsdonk et al. 2005). These findings notwithstanding, it is clear that species differences will be most pronounced in phylogenetically newest regions, some of which—e.g., frontal cortex—may be of most relevance to schizophrenia. As we attempt to interpret these circuit maps at higher levels of resolution to guide drug development—i.e., beyond simple efferent/afferent patterns, and down to the receptor- and subcellular levels—these cross-species differences may become increasingly important. A number of these differences are already suggested based on simple pharmacological challenge studies, described below.

Second, all rodent brains are not the same. Strain differences in PPI, and in sensitivity to drug effects on PPI, are quite remarkable across inbred and outbred rat strains, and across inbred and outbred mouse strains. These differences must reflect differences in the PPI-regulatory brain circuitry, potentially at any level from the presence of different cell types within a larger circuit organization, down to differences in the activity of specific enzymes within signal transduction pathways. Inbred Brown Norway rats exhibit significantly more PPI at short prepulse intervals and significantly less PPI at long prepulse intervals, compared to outbred Sprague Dawley (SD) rats (Swerdlow et al. 2006a). These differences are heritable (Swerdlow et al. 2008), and must reflect genetically mediated differences in brain organization. Albino SD and hooded Long Evans (LE) rats differ significantly in their sensitivity to the PPI-disruptive effects of dopamine (DA) agonists (e.g., Swerdlow et al. 2004a, 2006d) and in the expression of DA-regulatory enzymes [e.g., catechol-o-methyl transferase (COMT)] and signal transduction enzymes (e.g., protein kinase) within the nucleus accumbens (Shilling et al. 2008). Which of these strains provides an anatomical/neurochemical "map" of PPI that is most informative about human PPI circuitry, and hence, about PPI circuit abnormalities in schizophrenia? The answer is likely to differ, based on the neural systems and levels of resolution being studied, and the models being applied.

Treatment

It is reasonable to expect that studies of PPI in laboratory animals will continue to play a major role in the discovery and development of novel therapeutics for schizophrenia. As noted above, there is no compelling empirically based reason to expect that increased PPI per se might be desirable or functionally enhancing, nor that the ability of a drug to increase PPI in schizophrenia patients should be necessary or sufficient for clinical benefit. Despite this caveat, there is clear empirical evidence that the ability of drugs to "normalize" PPI levels after they have been reduced experimentally by specific drugs or perhaps by other manipulations (e.g., developmental manipulations) strongly predicts clinical utility and even potency of antipsychotic agents (Swerdlow et al. 1994; Swerdlow and Geyer 1998; Fig. 2). Towards this end, PPI has been used in several different types of predictive models, which differ in their sensitivity, specificity, logistical complexity, and even in the types of antipsychotics that they appear to identify. These issues are reviewed in Geyer et al. (2001), and an update of studies using PPI for its predictive validity since 2000 are found in Table 2.

The four most common variations of the PPI paradigm in models predictive of antipsychotic effects involve the use of (1) DA agonists (Fig. 2), (2) NMDA antagonists, (3) isolation rearing (IR), and (4) neonatal ventral hippocampal lesions (NVHLs). While each of these variations is based on a biological "construct" for the etiology of schizophrenia, i.e., hyperdopaminergia, hypoglutamatergia, and specific neurodevelopmental insults, they have all been applied towards predicting antipsychotic properties in novel compounds. In truth, only the former two variants are well suited to traditional "rapid throughput" drug screens, based on the amount of time and resources necessary for the developmental models, and the relatively small (and often strain- or sex-dependent) effects of isolation rearing on PPI (Weiss et al. 1999, 2000; Powell et al. 2002). In each of these variations, the ability of a drug to "normalize" PPI is interpreted as evidence for antipsychotic potential. Some second generation antipsychotics, such as clozapine, quetiapine, and olazapine, tend to increase PPI in otherwise intact animals (Swerdlow and Geyer 1993b; cf. Geyer et al. 2001), particularly in mice, adding some interpretative complexity to their ability to normalize PPI after pharmacological, developmental, or surgical manipulations. In fact, the ability to enhance baseline PPI is a signal that has been used as a predictor of antipsychotic potential in mice, in some normally "low-gating" mouse strains (cf. Ouagazzal et al. 2001a), rat strains (Feifel et al. 2001, 2004), and even in normal "low-gating" humans (Swerdlow et al. 2006a; Vollenweider et al. 2006).

Beyond the dopamine system, some new targets of antipsychotics have emerged in recent years, based in part on studies using variations of PPI paradigms as predictive models. Examples of these targets include (but are not limited to) selective 5-HT_{2C} receptor agonists (Marquis et al. 2007), CB1 cannabinoid receptor antagonists (Nagai et al. 2006), neurotensin-1 receptor agonists (Shilling et al. 2003, 2004; Caceda et al. 2005), selective adenosine A(2A) receptor agonists (Wardas et al. 2003), alpha-7 nicotinic receptor agonists (Suemara et al. 2004), and selective histamine H3 receptor antagonists (Fox et al. 2005; Table 2). It should be emphasized that in some cases, these targets were identified based on PPI assays with less compelling predictive validity, such as the ability of compounds to increase basal PPI levels in mice, or to normalize PPI after its disruption by 5HT agonists or NMDA antagonists. These assays may have strong sensitivity, particularly for identifying compounds with potentially novel mechanisms, but they also may lack specificity for detecting antipsychotic properties, at least in comparison to assays based on the ability to block the PPI-disruptive effects of apomorphine and perhaps other DA agonists (Fig. 2). We will have to await clinical evidence to determine whether these reports reflect "false positives" of these models.

PPI has only more recently begun to be used in models for detecting preventative or neuroprotective interventions, to identify strategies that would prevent the neuropathological and clinical consequences of a vulnerability gene or developmental insult involved in the prodrome and onset of schizophrenia. Some studies are approaching such an application, using early neuroimmune challenges to yield PPI deficits during adulthood (e.g., Borrell et al. 2002), or using sustained early life antipsychotic exposure to blunt the PPI-disruptive effects of developmental insults (Powell et al. 2006a, b). Assuming that these models succeed, it remains to be determined how one would test or apply such interventions in a clinical setting.

A reliable, robust, quantitative phenotype

In any given rodent species and strain, both PPI and its drug sensitivity are quite robust and reliable phenotypes. Within a range of 30–120 ms prepulse intervals, and 2–16 dB noise prepulses over a 65- to 70-dB(A) noise background, and 105–120 dB(A) noise pulses, PPI in rats exhibits a magnitude and parametric sensitivity that are strikingly similar across a number of studies from different laboratories and, conveniently, are also quite similar to those exhibited by humans. Similarly, PPI-disruptive effects of a number of simple manipulations (e.g., administration of a direct DA agonist) have been replicated across laboratories to the point that they have become “standard assays”, in predictive models for antipsychotic development. The PPI-disruptive effects of more complex manipulations, including early developmental lesions or isolation rearing, tend to be more variable across laboratories (discussed above), perhaps due to the complexities (and hence variability) of the methods and uncontrolled sources of variance. Some differences in reports of PPI drug sensitivity and sensitivity to developmental manipulations clearly seem to result from differences in rat strain or even supplier (e.g., Swerdlow et al. 1998, 2000b, 2003a, 2004a), and these differences are being explicated at the levels of heritable differences in neural substrates regulating PPI.

Some disparities in reported drug or other manipulation effects on PPI may also reflect differences in the recording properties of a variety of “home built“ and commercially available startle response acquisition systems. While there is no “gold standard” for such an apparatus, there are a number of characteristics that should be evaluated in interpreting whether response measurements “obey the laws of physiology”, e.g., intensity- and interval-dependence of PPI, and relative insensitivity of PPI to weight differences across animals. These issues are reviewed in Geyer and Swerdlow (1998).

Startle and PPI data can be deceptively complex, and some disparities in reported effects on PPI in rodents undoubtedly reflect these complexities and resulting interpretative differences across studies. Despite the impressive degree of automation in laboratory measures of PPI, one cannot automatically enter startle data into an equation and reasonably expect the calculated percent PPI to be informative. For example, we have previously reviewed the importance of considering the impact of changes in startle magnitude on changes in PPI (Swerdlow et al. 2000a). Simply put, the only unambiguous changes in sensorimotor gating are ones that can be demonstrated in the absence of changes in startle magnitude. In this case, reduced sensorimotor gating reflects a diminished impact of the prepulse on startle magnitude and, hence, an increase in startle magnitude on prepulse + pulse trials only. Any other related pattern of results, involving significantly reduced or increased startle magnitude on pulse-alone trials, must be interpreted in the context of additional supportive evidence. Such evidence might come from the use of low and high pulse intensities or from subgroups of rats that are matched based on comparable levels of startle magnitude.

Another interpretative issue that has been discussed in several recent reports relates to the potential impact of prepulse-induced startle activity on PPI and its modification by drugs or other experimental manipulations (Yee et al. 2004; Swerdlow et al. 2004c). A stimulus is only considered a “prepulse” in relationship to a second stimulus. By any other metric, it is simply a stimulus and can elicit motor activity including a startle reflex, depending on its properties. If the prepulse intensity exceeds the startle threshold, a “prepulse + pulse” configuration is better described as a “paired-pulse” configuration, and the resulting decrement in the startle response elicited by the second pulse is described as “paired-pulse inhibition”, comparable to the phenomenon used to study “blink excitability” (e.g., Kimura and Harada 1976; Valls-Sole et al. 2004). The similarities and differences of PPI and paired-pulse inhibition have been described for a small number of drug effects (e.g. Swerdlow et al. 2002a), but relatively little is known about this relationship for the long list of manipulations that have been applied towards PPI studies.

The interpretative ambiguities created by “prepulse-elicited startle” are most relevant to conditions in which the prepulse exceeds startle threshold. In a rat, for 20 ms noise prepulses over a 70-dB(A) noise background, this threshold is generally between 12 and 15 dB, although the precise value varies with strain, sex, age, and other factors. Other prepulse characteristics, including frequency (pure tone vs. white noise), duration, and configuration (continuous vs. discrete) can impact its motor-inhibiting and activating properties. For the vast majority of published PPI studies, prepulses are used at levels that elicit no or little detectable motor activity; even relatively intense prepulses (e.g., 10–15 dB salience, based on the stimulus conditions described above) might elicit a motor “signal” that is <1% of the total startle signal (Swerdlow et al. 2004c). In fact, this signal is comparable to that detected on "NOSTIM" trials, i.e., when no motor activity is recorded in the absence of stimulus delivery, suggesting that this small signal reflects ongoing motor activity rather than a prepulse-elicited motor response (e.g. Swerdlow et al. 2004c; Weber and Swerdlow 2008). Importantly, only a small fraction of studies utilize prepulses with suprathreshold intensities, and among these, most also utilize much weaker prepulses as internal comparisons. PPI is used to assess many things, and in some cases, a range of prepulse intensities is used to create a complete parametric characterization for purposes unrelated to drug effects (e.g., QTL analyses). Clearly, in these cases, the use of intense prepulses is not a "confound", but simply a way to fully characterize a phenotype.

It is argued that potentially confounding effects might arise if a drug or other manipulation lowers startle threshold and, hence, transforms a non-startling prepulse into one that elicits a motor response (Yee et al. 2004). Specifically, a potentially confounding interaction might arise if increases in prepulse-evoked motor responses diminished the prepulse's inhibitory effects on a subsequent startle response. In fact, there is no reason to predict such an effect: full startle responses elicited by an S1 in a paired-pulse paradigm do not interfere with the inhibitory impact of S1 on the startle response to S2 (e.g., Swerdlow et al. 2002a), so there is no credible reason to predict that such interference would result from a prepulse-evoked response that is 100-fold less intense. Nonetheless, under drug conditions, a number of control comparisons can be conducted—analogous to those used to understand the impact on PPI of drug-induced changes in startle magnitude—to determine whether drug effects on prepulse-evoked motor activity and PPI can be "dissociated". We might predict that a common drug receptor (e.g., D1 or D2) might mediate two processes (reduced PPI and increased prepulse-induced motor activity), via effects within different brain substrates. Similar to changes in startle magnitude, a given drug might elicit either increases, decreases, or no change in prepulse-induced motor responses, yet have a consistent effect on PPI (e.g., Weber and Swerdlow 2008); even in cases where drug-induced changes in prepulse-induced activity are detected, they amount to shifts of less than 1% of the total "signal" of the startle response and, as noted above, are comparable to changes observed in "NOSTIM" activity. Thus, while it is a reasonable precaution to consider measuring prepulse-elicited motor activity to ascertain whether it is significantly greater than ongoing background motor activity, and whether it might potentially interact with the startling effects of the startle pulse, in our experience, such an exercise amounts to "much ado about [almost] nothing" (Swerdlow 2005).

A useful tool for modeling the neurobiology and gating and its deficits in humans

The most compelling contribution of animal studies of PPI towards the understanding of the basis for PPI deficits in schizophrenia comes in the ability to directly manipulate neural and genetic substrates and test hypotheses in a controlled experimental setting. The challenges of extrapolating such findings across species are not trivial, as discussed above in relationship to neural circuit maps. Still, for understanding the contribution to PPI deficits in schizophrenia of pathology in medial prefrontal cortex, hippocampus, amygdala or ventral striatum, or of specific candidate genes or early developmental insults, cross-species studies are a unique, powerful tool.

PPI studies have also identified neurobiological bridges across species that may reveal potential limitations of these studies and, perhaps, more generally of animal models of schizophrenia. For example, several drugs potently disrupt PPI in rats and yet increase PPI in normal humans. This is most notable because the drugs in question—ketamine (Abel et al. 2003; Duncan et al. 2001), MDMA (Vollenweider et al. 1999) and under some conditions, DA agonists (Bitsios et al. 2005)—have pharmacological and clinical properties that are central to models for the pathophysiology of schizophrenia. These findings raise both experimental and conceptual issues.

At an experimental level, drug doses, routes of administration, and pharmacokinetic/dynamic properties differ substantially across species. As one example, amphetamine reliably decreases PPI in rats only at doses above 2 mg/kg administered subcutaneously (Mansbach et al. 1988; Sills 1999; Swerdlow et al. 2006d), while the oral dose of amphetamine given to normal humans in PPI studies rarely exceeds 0.29 mg/kg (20 mg total; e.g., Hutchison and Swift 1999; Swerdlow et al. 2003b). Species differences in drug effects might also reflect contextual differences in the test setting. Humans volunteer and are paid for study participation, have the test conditions explained by a supportive research assistant, swallow a pill, and sit in a comfortable chair during testing; by contrast, rats are removed from a cage, injected with a drug, and then placed alone in a plastic tube inside an unfamiliar box where they are exposed to loud, unexpected noises. One might imagine that drug effects on a fight-or-flight reflex (startle) might differ in these two conditions, independent of species. Furthermore, while the parametric properties of PPI (e.g., sensitivity to prepulse intensity and interval) are strikingly similar across species, drug effects might reveal some cross-species differences in these parametric effects. For example, at 120 ms prepulse intervals, ketamine has opposite effects on PPI in rats (disrupts PPI; Mansbach and Geyer 1989) and humans (increases PPI; Abel et al. 2003; Duncan et al. 2001);

on the other hand, ketamine can increase PPI in rats at shorter prepulse intervals (e.g., 30 ms; Mansbach and Geyer 1989). Our group has detected similar species- and interval-dependent effects with the NMDA antagonist, memantine (Swerdlow et al. 2003c, 2005a). Conceivably, NMDA-related mechanisms of drug effects on gating at 30 ms in rats might best approximate those at 120 ms in humans.

However, this explanation does not address the conceptual dilemma created by the fact that psychotomimetic drugs increase PPI in normal humans, while schizophrenia is associated with reduced PPI. While PPI deficits in schizophrenia might possibly reflect the consequences of sustained deficiencies in glutamatergic activity in the context of developmentally aberrant neural connections, it does not follow that such effects would be reproduced by an acute challenge of an NMDA antagonist to a normal individual with normal neural connectivity. Furthermore, one might easily imagine that acute drug effects on an intact brain might enhance sensorimotor gating via a mechanism that is very distinct from (e.g., “upstream” or “downstream” from) those responsible for reduced gating in the brain of a schizophrenia patient. Nonetheless, faced with these discrepant effects of psychotomimetic drugs on PPI, it is difficult to know whether the failings lie in the cross-species translation of the PPI model, in the validity of the acute ketamine/glutamate antagonist model of schizophrenia, or both.

An additional challenge in building neurobiological bridges of PPI studies across species comes from the human side of the bridge—from the observations that drug effects on PPI in humans can differ significantly, depending on basal levels of PPI. A number of drugs—including amphetamine (Swerdlow et al. 2003b), pergolide, amantadine (Bitsios et al. 2005), quetiapine (Swerdlow et al. 2006a), and clozapine (Vollenweider et al. 2006)—have been demonstrated to have effects that differ significantly (and in some cases, are arithmetically opposite) in normal humans with low vs. high PPI levels, relative to the overall test population. Similar findings may be emerging from animal studies, e.g., among inbred strains with low basal levels of PPI (cf. Ouagazzal et al. 2001a). How we interpret this “rate dependency” of drug effects on PPI in humans and laboratory animals and what it means about the many reported drug effects on PPI that have not considered or tested the impact of basal PPI levels, are issues that remain to be resolved.

While this discussion has focused primarily on cross-species comparisons between rodents and humans, and we discussed earlier the strain differences in PPI that have been detected in both rats and mice, it is also worth noting that there are also a number of important cross-species differences in PPI and its parametric and pharmacological sensitivity between rats and mice. Just as one example, while PPI is disrupted by DA agonists in both rats and mice, there is some evidence that this effect primarily reflects activation of D2 receptors in rats (Swerdlow et al. 1994; cf. Geyer et al. 2001), but of D1 receptors in mice (Ralph-Williams et al. 2003a; Ralph and Caine 2005). Within a restricted set of stimulus parameters (particularly prepulse intervals), infusion of D2 agonists into the nucleus accumbens *decreases* PPI in rats and *increases* PPI in mice (Mohr et al. 2007). This issue is not yet settled, as mice lacking D2 receptors are insensitive to the PPI-disruptive effects of *d*-amphetamine (Ralph et al. 1999), and some mouse strains exhibit “rat-like” PPI sensitivity to D2 agonists (Ralph and Caine 2007). Nonetheless, enough data exists that we can be fairly confident that a similar drug effect on PPI in rats and mice does not necessarily reflect a common underlying brain substrate. This raises the dilemma that when modeling the loss of PPI in schizophrenia, we are almost certainly studying very different neurobiological substrates, depending on the model species; this makes it very difficult to identify a clear, a priori rationale for selecting one species over another.

A surrogate measure for neural processes with wide-reaching psychological implications

Models of higher cognitive processes are only now being developed in rodents. Given the limited size and processing capacity of the frontal cortex in mice and rats vs. primates, and its relatively weaker contribution to the organization of behavior, there is reason to be skeptical that rodent models of higher cognitive processes will provide meaningful homology to human cognition. Nonetheless, mice and rats are amenable to complex conditioning schedules and are capable of performing choices and sophisticated behavioral sequences, and it is certain that studies will assess the potential relationship of PPI to these processes (e.g., Roegge et al. 2007; Depoortere et al. 2007a, b; Garner et al. 2007; Paine et al. 2007). Extrapolating these findings to humans will present many challenges. In general, the farther forward one moves in the brain, the greater the anatomical and functional differences between rodents and humans. For example, one might imagine a scenario in which “cognitive” control in rodents involves a prominent role for subcortical (e.g., basal ganglia) functions that overlap with PPI-regulatory circuitry, while in humans, higher cognitive control is “encephalized” to discrete frontal circuits that participate less in the regulation of startle gating.

There is already some evidence for both convergence and divergence of PPI and other operational animal models of “gating”, in terms of their underlying neural substrates. For example, contemporaneous measures of PPI and N40 gating—an animal model of P50 ERP gating in humans—revealed that apomorphine, phencyclidine, and DOI each disrupt PPI and reduce ERP responsivity to the S1 stimulus in the N40-gating paradigm, but do not specifically disrupt N40 gating per se (Swerdlow et al. 2006b). Some overlap has been reported in the pharmacological sensitivity of PPI and [some of the various forms of] latent inhibition to DA agonists and NMDA antagonists (Mansbach and Geyer 1989; Bakshi et al. 1995; Razoux et al. 2007), although many conditions lead to a loss of PPI in rats but leave latent inhibition intact (e.g., amphetamine withdrawal (Peleg-Raibstein et al. 2006a, b) and D2 blockade in the basolateral amygdala (Stevenson and Gratton 2004)). Thus, neurobiological mechanisms of PPI cannot be assumed to be common to experimental measures of either sensory or cognitive gating in rats. The potential overlap in the neurobiology of PPI and higher-order functions in rats, such as working memory, is an area of ongoing investigation. At present, there is no compelling evidence that such an overlap exists or that PPI is informative about higher cognitive functions in rodents.

Summary: animal studies

Animal models will remain an important tool in developing and testing hypotheses for the pathogenesis of brain disorders. As a reliable, quantitative "read out" of relatively well-defined neural circuitry, measures of PPI in laboratory animals will continue to be used to test and validate these hypotheses and to generate important new hypotheses regarding cellular mechanisms and therapeutic strategies. PPI models provide predictive validity in drug discovery and development, both as rapid through-put screens and as components of more biologically sophisticated models involving developmental, immunologic, and genetic manipulations. Areas of convergence and divergence are being identified in the cross-species pharmacology of PPI; areas of convergence will be exploited so that human drug effects can be predicted and understood based on PPI drug effects in rodents and their underlying cellular and molecular substrates. Finally, the relationship of PPI to higher-order learning processes is being explored in rodents, and the findings will be used to generate and test hypotheses regarding the interplay of sensorimotor gating and cognition in normal and disordered humans.

Conclusions

The construct of gating deficits in neuropsychiatric disorders has empirical support and intuitive appeal, and serves as a unifying heuristic for understanding the psychological and neural substrates shared by otherwise apparently unrelated disorders. PPI is an operational measure of basic, brain-based gating processes. It is robust, reliable, easily quantified, and versatile as an experimental tool, and is abnormal in several brain disorders including schizophrenia, that are characterized by clinical evidence of impaired gating of sensory, cognitive, motor of affective information. PPI can be measured across species and is regulated in laboratory animals by neurochemical, anatomical, developmental, and genetic substrates that can be systematically studied and used as the basis for developing and testing hypotheses for the biological basis of PPI deficits in patients.

For all of these reasons, studies of PPI in humans and laboratory animals have multiplied and expanded, and this measure is being used to explore many new questions at many different levels of analysis. While our field does not yet face the floods of the "Sorcerer's Apprentice" (von Goethe 1779), it is clear that findings have amassed at an exponential rate and are testing our collective ability to critically integrate results, to identify areas of consistency, redundancy, and disagreement. Based on a review of the present literature, we reached several conclusions: (1) in humans, PPI is not "diagnostic"; levels of PPI do not predict clinical course, specific symptoms, or individual medication responses; (2) in preclinical studies, PPI is valuable for evaluating models or model organisms relevant to schizophrenia, "mapping" neural substrates of deficient PPI in schizophrenia, and advancing the discovery and development of novel therapeutics; (3) across species, PPI is a reliable, robust quantitative phenotype that is useful for probing the neurobiology and genetics of gating deficits in schizophrenia. In this review, we also identify some realistic expectations of this paradigm, describing its considerable strengths but also limitations, and stress some interpretative issues for consideration as we move forward with this powerful tool for translational neuropsychiatric research.

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