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REVIEW

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Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies

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Abstract *Rationale:* Since the mid-1970s, cross-species translational studies of prepulse inhibition (PPI) have increased at an astounding pace as the value of this neurobiologically informative measure has been optimized. PPI occurs when a relatively weak sensory event (the prepulse) is presented 30–500 ms before a strong startle-inducing stimulus, and reduces the magnitude of the startle response. In humans, PPI occurs in a robust, predictable manner when the prepulse and startling stimuli occur in either the same or different modalities (acoustic, visual, or cutaneous). *Objective:* This review covers three areas of interest in human PPI studies. First, we review the normal influences on PPI related to the underlying construct of sensori- (prepulse) motor (startle reflex) gating. Second, we review PPI studies in psychopathological disorders that form a family of gating disorders. Third, we review the relatively limited but interesting and rapidly expanding literature on pharmacological influences on PPI in humans. *Methods:* All studies identified by a computerized literature search that addressed the three topics of this review were compiled and evaluated. The principal studies were summarized in appropriate tables. *Results:* The major influences on PPI as a measure of sensorimotor gating can be grouped into 11 domains. Most of these domains are similar across species, supporting the value of PPI studies in translational comparisons across species. The most prominent literature describing deficits in PPI in psychiatrically defined groups features schizophrenia-spectrum patients and their clinically unaffected relatives. These findings support the use of PPI as an endophenotype in genetic studies. Additional groups of psychopathologically disordered patients with neuropathology involving cortico-striato-pallido-pontine circuits exhibit poor gating of motor, sensory, or cognitive information and corresponding PPI deficits. These groups include patients with obsessive compulsive disorder, Tourette's syndrome, blepharospasm, temporal lobe epilepsy with psychosis, enuresis, and perhaps post-traumatic stress disorder (PTSD). Several pharmacological manipulations have been examined for their effects on PPI in healthy human subjects. In some cases, the alterations in PPI produced by these drugs in animals correspond to similar effects in humans. Specifically, dopamine agonists disrupt and nicotine increases PPI in at least some human studies. With some other compounds, however, the effects seen in humans appear to differ from those reported in animals. For example, the PPI-increasing effects of the glutamate antagonist ketamine and the serotonin releaser MDMA in humans are opposite to the PPI-disruptive effects of these compounds in rodents. *Conclusions:* Considerable evidence supports a high degree of homology between measures of PPI in rodents and humans, consistent with the use of PPI as a cross-species measure of sensorimotor gating. Multiple investigations of PPI using a variety of methods and parameters confirm that deficits in PPI are evident in schizophrenia-spectrum patients and in certain other disorders in which gating mechanisms are disturbed. In contrast to the extensive literature on clinical populations, much more work is required to clarify the degree of correspondence between pharmacological effects on PPI in healthy humans and those reported in animals.

Keywords Prepulse inhibition · Startle · Information processing · Schizophrenia · Obsessive compulsive disorder · Tourette's syndrome · Antipsychotic medications

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Introduction

Prepulse inhibition (PPI) of the startle response is a measure of inhibitory function and time-linked information processing by which a weak sensory stimulus (the prepulse) inhibits the elicitation of the startle response caused by a sudden intense stimulus. PPI is commonly viewed as an operational measure of a process called "sensorimotor gating", by which excess or trivial stimuli

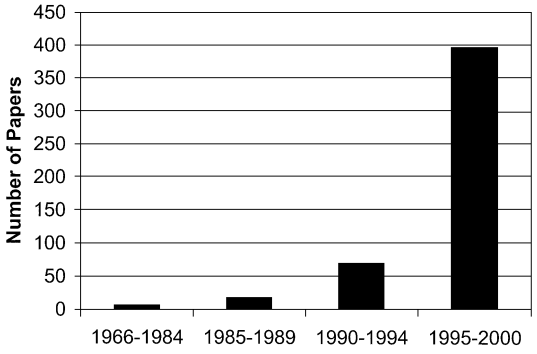

Fig. 1 Citations of human and animal model PPI studies from 1966 to 2000 (sourced from Medline)

are screened or "gated out" of awareness, so that an individual can focus attention on the most salient aspects of the stimulus-laden environment (Braff and Geyer 1990). Since the mid-1970s, cross-species translational studies of PPI have increased at an astounding pace (see Fig. 1) as the value of this neurobiologically informative measure has been optimized. The first section of this review addresses parametric features of PPI that are crucial in interpreting the studies presented in the next two sections of this paper (PPI in psychopathological groups and pharmacological studies).

From an historical perspective, theories at first focused on the concept that information is processed through a series or sequence of "steps" or "stages" in a framework of sequential processing of informational stimuli. These serial, hierarchically arranged operations were thought to occur at progressively "higher" sites in the central nervous system. Abnormalities of information processing were conceptualized as occurring at various stages, resulting in dysregulation and dysfunction across a spectrum of cognitive operations and associated behaviors (Braff et al. 1991). For example, psychotic patients were viewed as having deficits in the early stages of information processing (e.g. sensory registration and early processing) which, in turn, led to a cascade of "downstream" deficits in cognitive integration, and ultimately to clinical symptoms and functional impairment (cf. Venables 1960; Braff 1985, 1993, 1999; Braff and Geyer 1990). These "stage" models then were increasingly challenged by a new generation of alternative "integrationist" models, that rely on neural network theory, which emphasizes that cascades of neurons in multiple loci create an integrated "symphonic array" of time-coordinated events across multiple sites (Braff 1999). This integrated, multi-site activity or neural circuit is thought to be impaired in schizophrenia and other psychiatric disorders (Swerdlow and Koob 1987; Andreasen 1999; McGlashan and Hoffman 2000).

The startle reflex consists of a contraction of the skeletal and facial muscles in response to a sudden, relatively intense stimulus that may be presented across multiple modalities (visual, auditory, or tactile). This reflex is usually classified as a special subtype of a defensive (as opposed to an orienting) response (Turpin 1986). One major advantage of the startle reflex paradigm in psychopathology and psychopharmacology research is that it can be studied across species, lending itself to translational research opportunities (Geyer and Braff 1987; Braff and Geyer 1990; Geyer et al. 2001, this issue; Swerdlow et al. 2001d, this issue). In humans, the eyeblink component of startle is typically measured using electromyography (EMG) of the orbicularis oculi muscle (Graham 1975). In rats and mice, stabilimeter chambers measure the whole-body flinch elicited by stimuli that are similar (or identical) to those used in humans. Most importantly, the startle response also demonstrates several important forms of plasticity that are also exhibited across species, including PPI (Graham 1975), habituation (Hoffman and Searle 1968; Geyer and Braff 1987), and fear potentiation (Brown et al. 1951) that are regulated by the forebrain and related structures. Thus, startle plasticity is an ideal candidate for translational research, as is illustrated in this review and the two reviews that follow (Geyer et al. 2001; Swerdlow et al. 2001d, both this issue). One form of startle plasticity, "prepulse inhibition" (PPI), is the normal suppression of the startle reflex that occurs when the intense startling stimulus (e.g. a 115 dB noise burst) is preceded by a relatively weak prestimulus, as reviewed by Graham in her Presidential Address to the Society for Psychophysiological Research and the review article that accompanied her address (Graham 1975). In order to inhibit startle, the prepulse stimulus must precede the startling stimulus by 30–500 ms (Hoffman and Wible 1969; Graham 1975; Hoffman and Ison 1980; Ison and Hoffman 1983).

In PPI, the weak sensory event (the prepulse) inhibits ("gates") the startle motor response to a startling stimulus; hence we use the term "sensorimotor gating" to describe the construct measured by PPI. PPI is a ubiquitous and robust experimental phenomenon: it occurs when the prepulse and startling stimuli are in the same or different sensory modalities (Blumenthal and Gescheider 1987; Graham 1980; Hoffman and Ison 1980). It occurs in all mammals, and it is not a form of conditioning, because it occurs on the first exposure to the combination of prepulse and pulse stimuli (Blumenthal et al. 1996), and does not exhibit habituation or extinction over multiple trials. PPI is a stable neurobiological marker: PPI measurements repeated at one-month intervals for 3 months in ten normal adult males yielded intraclass correlations of 0.94 when relatively salient prepulses were used [e.g. 16 dB(A) over background; Cadenhead et al. 1999]. The prepulse has inhibitory influences that can be regulated by connections between limbic cortico-striato-pallido-pontine (CSPP) and related cortico-striato-pallido-thalamic (CSPT) circuitry, and the primary startle circuit within the pons (cf. Swerdlow and Koob 1987; Swerdlow et al. 1992; Lee et al. 1996). Thus, PPI reflects the activation of behavioral gating processes that are regulated by forebrain neural circuitry. This circuitry exerts a regulatory influence, but the signal of the prepulse need not traverse the CSPP circuitry (i.e. mediate via the forebrain circuits) in order to produce PPI (Davis and Gendelman

1977). The forebrain circuitry modulation of PPI has been the target of many animal studies, described in an accompanying article (Swerdlow et al. 2001d, this issue).

In order to elicit PPI, a weak prepulse stimulus activates brain-based processes that blunt responsivity to sensory events during a subsequent relatively brief temporal window. The temporal limits of the time period of "gating" attributed to the prepulse are empirically determined to be approximately 30–500 ms in duration, in both humans and rats (Hoffman and Searle 1968; Graham 1975). Prepulse-to-pulse intervals of 30–240 ms are typically utilized in human PPI experiments, with maximal amplitude inhibition generally occuring with intervals of approximately 120 ms. The period of reduced responsivity following the prepulse has been postulated transiently to "protect" information contained in the weak stimulus, so that it can be adequately processed, without interference from the subsequent strong or disrupting startling stimulus (Blumenthal et al. 1996; Swerdlow et al. 1999a).

PPI is studied in the laboratory, but under "natural" circumstances, the process of sensorimotor gating is conceptualized as helping the organism to regulate environmental inputs, to navigate successfully in a stimulus-laden world, and to selectively allocate attentional resources to salient stimuli (Swerdlow 1996; Braff 1999; Granholm et al. 1999). Typically, the specific characteristics of an individual's gating processes are viewed as being plastic and to have both state and trait determinants influenced by a combination of environmental and genetic factors. Thus, as discussed below, PPI is viewed as being trait related (Cadenhead et al. 1993) and is also sensitive to developmental factors, such as neonatal insult (Lipska et al. 1995) or social isolation (Geyer et al. 1993), and perturbations as well as toxic influences of the neurochemical and hormonal milieu of the nervous system (cf. Swerdlow et al. 2000b).

Parametric influences on PPI

This paper is designed to present human research that articulates with the accompanying animal model translational papers (Geyer et al. 2001; Swerdlow et al. 2001d, both in this issue). In this context, human studies of PPI have identified a number of normally occurring influences on PPI, as discussed below. These parametric influences are crucial factors in designing and interpreting human psychopathological and pharmacological studies, as well as animal model experiments discussed in the two accompanying articles.

Prepulse salience

Typically, an acoustic prepulse arises out of a continuous background noise so that one aspect of the salience of the prepulse is a reflection of the difference between background noise level and prepulse noise level, measured in decibels and complementary sound pressure levels (SPL). Accordingly, the intensity of the prepulse is often specified in terms of dB above background noise (e.g. Mansbach et al. 1988; Davis et al. 1990; Swerdlow et al. 1993a; Braff et al. 1999, 2001).

In general, stronger or more salient prepulses induce greater levels of PPI (e.g. Hoffman and Wible 1970; Reiter and Ison 1977; Sanes and Ison 1979; Grillon et al. 1992; Swerdlow et al. 1993a). Despite this general rule, the specification of the strength of the prepulse is not as straightforward as it might appear at first. For example, although a startle-eliciting stimulus typically is presented at the level of 100–115 dB(A) SPL, the prepulse is usually conceptualized as "arising" out of a specified level of background noise. This factor becomes a difficult confound when background noise in an experiment is not well controlled or is not even reported. For example, in some studies of PPI deficits in psychiatric populations, prepulses "arise" from an uncontrolled ambient background level of 30–40 dB, while in other studies, prepulses are superimposed on a white or broadband noise level typically specified at the 70 dB level. When background levels differ to this degree, the effective intensity of a prepulse can differ by as much as 40 dB. Clearly, it cannot be assumed that the exact same brain processes regulate PPI using prepulse intensities that effectively differ by as much as 40 dB above background noise.

Across most commonly used background noise levels (e.g. 70 dB), there is an orderly relationship between prepulse intensity and amount of PPI, for prepulses below levels that independently elicit a startle reflex (e.g. Berg 1973; Blumenthal and Goode 1991; Braff et al. 1999). Blumenthal (1995, 1996) has also shown that the intensity of the startle eliciting stimulus as well as the intensity and duration of the prepulse can affect PPI; PPI increases with both prepulse intensity and duration which follows Bloch's law that stimulus salience reflects an interaction of intensity and duration. A separate literature of studies has investigated the phenomenon of "pulse-pulse" (or "condition-test") inhibition, in which the startle reflex response to a startling stimulus (typically electrocutaneous) is inhibited when the startling pulse is preceded immediately (e.g. 100 ms) by an equally intense stimulus (e.g. Smith and Lees 1989). The degree to which pulse-pulse inhibition and PPI reflect similar or different brain processes is not currently known. Accordingly, the appropriate and standard practice in the literature is to use the term "prepulse inhibition" only for conditions in which the prepulse does not elicit a startle response.

Prepulse-to-pulse intervals: magnitude and latency effects

In human studies, the onset of the prepulse to the onset of the pulse interstimulus-intervals (ISI) typically range from between 30 to 240 ms for eliciting PPI. [Note: in many studies, particularly those using continuous rather than discrete prepulses (see below), the term "stimulus onset asynchrony" (SOA) is used in place of "ISI".] ISI

intervals of 1000 ms or more can elicit facilitation of the human startle response magnitude (Hoffman and Wible 1969; Graham 1975; Graham et al. 1975; Braff et al. 1978; Harbin and Berg 1983). Thus, a major strength of PPI paradigms is that it is possible to assess both reflex inhibition and facilitation in a single test session, using short (e.g. 30–120 ms) and long (e.g. >1000 ms) ISIs, respectively (see Fig. 2). Although much of the PPI literature stresses the magnitude of the observed startle reflex, it should be noted that there are prestimulus effects on latency of the startle response that are quite important. The latency-to-startle onset and latency-to-startle peak are measures of the rapidity with which the startling stimulus elicits the startling response. Prepulse-to-pulse ISIs have somewhat differential effects on startle magnitude and latency. First, under specific experimental conditions, ISIs of 60–120 ms elicit maximal PPI-related amplitude reduction in normal human subjects (Braff et al. 1978; Ison and Pinckney 1983). In contrast, the ISIs that maximally facilitate (shorten) startle latencies are briefer (i.e. 30 ms; Graham 1975; Braff et al. 1978, 1992). Thus, there are experimental design issues for studying magnitude diminution and latency facilitation: a typical experimental design for studying prestimulus effects on both reflex magnitude inhibition and latency facilitation might utilize 30, 60, and 120 ms prepulse intervals, with expected maximal latency facilitation at 30 ms and maximal magnitude inhibition at 120 ms (e.g. Braff et al. 1978).

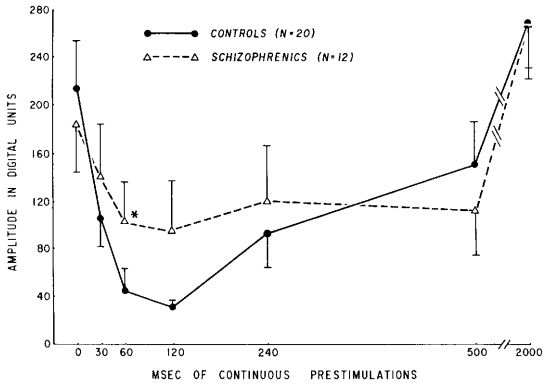

Fig. 2 Amplitude of blink reflex for normal subjects and schizophrenia patients

Inter-trial intervals

The effects of the interval between successive stimulus trials (pulse alone or prepulse+pulse pairs) has received little attention, especially in the psychopathological and neuropharmacological literature in humans. In general, typical inter-trial intervals (ITIs) center around 15–20 s with a range of 8–30 or more seconds (e.g. Braff et al. 1978, 1999). Variable ITIs promote less reflex habituation, compared to fixed ITIs, and thus allow measures of PPI when startle magnitude is both more robust and more stable.

Sex differences

Sex differences have begun to be carefully examined in PPI paradigms in normal and psychiatrically disordered human subjects over the past decade. There is convincing evidence that adult males have more robust PPI than do adult females under certain experimental conditions (e.g. Swerdlow et al. 1993b). In children, Ornitz et al. (1991) reported a complex, variable pattern of PPI starting early in life with greater PPI in boys versus girls by age 8 years. Blumenthal and Gescheider (1987) reported greater startle reflex probability in women versus men on prepulse+pulse trials, which might also reflect relatively greater PPI in men compared to women. In females, the level of PPI across the menstrual cycle appears to be variable (Swerdlow et al. 1997a). For example, Swerdlow et al. (1997a) identified a "nadir" of PPI levels during the mid-luteal phase, at a time of maximally elevated estrogen and progesterone levels. Conceivably, this finding might be related to other cognitive and psychophysiological measures that show cyclical changes across the menstrual cycle in females (Kimura and Hampson 1993). Clearly, it is important to consider the potential impact of hormonal (and potentially other) sex-related factors on PPI in clinical populations. These influences are made more important by the complex influences of antipsychotic agents on endocrine function (see below).

An important theme that has never been explored in the literature is the possibility that monthly cyclical alterations in PPI among normal women may be associated with a more flexible and less "fixed" cognitive style. In terms of non-linear dynamical analyses where fixity is often associated with ill health (Winfree 1983; Paulus et al. 1996), this conceptualization fits the generally accepted idea that females with schizophrenia have milder and less severe and disabling forms of the illness than do males (Seeman and Hauser 1984; Angermeyer et al. 1990; Hass et al. 1990; McGlashan and Bardenstein 1990) (also see below). The generally accepted greater symptomatic, cognitive, and functional outcome virulence of schizophrenia in males than females may accrue from the fact that males are used to a higher fixed level of inhibition that collapses with the onset or exacerbation of the disorder, whereas females show a relative protection from these responses to inhibitory collapse because they are more accustomed to fluctuating and lower average levels of cyclical sensorimotor inhibition. These issues will undoubtedly need to be explored in future research.

Laterality

In early PPI studies, potentiometers were mounted on headbands and connected by threads to the eyelid (Graham 1975; Braff et al. 1978; Geyer and Braff 1982). Eyelid displacement was then assessed as a measure of the blink reflex component of the startle response. Over the years, almost all laboratories have converted to mea-

suring electromyographic (EMG) responses of the orbicularis oculi muscles (e.g. Braff et al. 1992). Some evidence has supported a normal lateralization in blink reflex magnitude (right>left) (Hager and Ekman 1985), and until recently, researchers have generally chosen unilateral right versus left blink measurement of the startle reflex. For a variety of reasons, it has become apparent that the choice of right versus left eyeblink measures might be an important factor in identifying abnormalities in specific psychiatrically disordered populations, in which dysfunction in the startle regulatory circuitry might be lateralized. For example, Swerdlow summarized a series of studies in which acoustic PPI in obsessive compulsive disorder (OCD) patients was reduced compared to control levels when PPI was recorded from the right orbicularis oculi, but not when it was recorded in separate subjects from the left orbicularis oculi (Swerdlow et al. 1997b). However, the failure to detect reduced PPI in OCD subjects from left eyeblink measures was confounded by the fact that control subjects exhibited significantly lower levels of left versus right eyeblink PPI; thus, it was not possible to determine whether this lateralized pattern of deficits reflected lateralized brain abnormalities in OCD patients, or instead, whether it reflected "floor" effects of more generally reduced left versus right eyeblink PPI. Laterality issues in PPI measures may even be important in parametric studies of PPI in normal individuals, because it is not clear that the many factors that impact PPI (e.g. prepulse intensity, interval, duration) do so equally to PPI assessed from right and left eyeblink responses.

More recently, investigators have begun to utilize bilateral blink recording. This addition has improved our ability to assess what may be a measure of left and right brain functioning crucial to normal cognitive and neuropathological processes, and has begun to yield interesting patterns of results. For example, Cadenhead et al. (2000) measured PPI of the acoustic startle response bilaterally in schizophrenia patients, their relatives, schizotypal personality disorder (SPD) individuals, and normal controls. The normal comparison subjects demonstrated greater PPI in the right eye, as described above (Swerdlow et al. 1997b). Also as described above in unilateral blink measures with OCD subjects (Swerdlow et al. 1997b), both the schizophrenia patients and their relatives had significantly decreased PPI when measured from the right eye, but not the left eye, compared to normal control subjects. By measuring bilateral blink recordings within subjects, Cadenhead et al. (2000) were able to demonstrate that, compared to the normal controls, schizophrenia patients, their relatives, and SPD patients showed less right-left PPI asymmetry. Conceivably, this pattern may reflect lateralized, left hemispheric dysfunction of schizophrenia patients (Gur and Chin 1999). The use of bilateral EMG measurement of PPI may allow us to further examine the relationship between left and right hemispheric functioning in normal subjects and in psychiatric disorders in which PPI deficits are observed.

Blink rates

Most of the literature on human startle involves the involuntary elicitation of a rapid onset, relatively brief blink reflex by an intense, abrupt stimulus that is fairly easily distinguished from slower onset, longer, voluntary, non-reflexive blinks. It is important to note that studies of eyeblink startle and PPI generally utilize specific waveform acquisition criteria that exclude these spontaneous non-reflexive eyeblinks (cf. Braff et al. 1978), to diminish the potential impact of group differences in spontaneous blink rates. Certainly, there is also interest in measures of spontaneous blink rates in psychiatric populations, because these rates are regulated at least in part by the dopamine system (Bodfish et al. 1995; Chen et al. 1996; Jacobsen et al. 1996; Vreugdenhill et al. 1997), and are increased in schizophrenia patients, perhaps reflecting elevated subcortical dopamine tone (e.g. Karson et al. 1990).

Attentional manipulations

Psychophysiological techniques frequently measure the automatic or "non-volitional" physiological response of human subjects in a specific paradigm, versus volitional or controlled processing of information (Callaway and Naghdi 1982). Sometimes (intentionally or unintentionally), various paradigms measure a complex mixture of both automatic and controlled information processing. Under some experimental conditions, PPI is reported to be increased when human subjects direct their attention towards a prepulse. This "attentional modulation" can be accomplished in a variety of ways, including asking subjects to "attend to" the presence of a prepulse, reinforcing prepulse detection (with tokens or money), or by manipulating specific prepulse stimulus characteristics (e.g. Dawson et al. 1993; Filion et al. 1993; McDowd et al. 1993). In normal subjects, these attentional influences occur only at longer interstimulus intervals (>120 ms), but not at prepulse intervals less than 120 ms (Dawson et al. 1993; Filion et al. 1993). These findings underscore one strength of the PPI paradigm: it appears to be amenable to the parsing of attention into voluntary versus automatic processing (Callaway and Naghdi 1982). Unfortunately, the elicitation of increased PPI via these strategies has not proven to be easily reproduced using various related attentional modulation paradigms (cf. Braff et al. 1997). It is very likely that the brain mechanisms regulating "attentional" versus automatic (uninstructed) forms of PPI differ substantially, with attention-induced changes reflecting the involvement of brain substrates regulating a range of processes, from motivation and volition to attentional allocation. Given the potentially complex psychological underpinnings of such processes, the attentional modulation of PPI presents significant challenges for cross-species studies, compared to models of the "uninstructed", automatic regulation of PPI. For these reasons, studies described in this manuscript, and

in the accompanying two papers, will focus on unstructed PPI.

Prepulse type

A variety of prepulse types have been used in studies of PPI. In general, prepulses can be either discrete (i.e. have an onset and offset followed by a "gap" of baseline noise level prior to the startle stimulus – a so-called "twin peak" configuration), or continuous (i.e. a sustained elevation of background noise, on which a startle stimulus is superimposed, without any offset of the prepulse or background "gap" – a so-called "peak on pedestal" configuration). Prepulses can also consist of white noise (comparable to both background and startle stimulus noise) or pure tones. Often in the literature, PPI results are compared and contrasted, without full consideration of these differences in prepulse characteristics, or their potential impact on PPI levels, or PPI differences between clinical and normal control populations. There is an emerging consensus that discrete white noise prepulses elicit maximal levels of PPI in both normal comparison subjects (e.g. Wynn et al. 2000) and schizophrenia patients (Braff et al. 2001). In parallel, in studies of some psychopathological groups, maximal effect size differences from normal comparison subjects occur when discrete white noise prepulses are utilized (discussed below; Braff et al. 2001).

Percent versus difference scores

In human and animal work, both percent and arithmetic difference scores have been utilized to quantify the amount of PPI. Percent scores quantify PPI based on the percent reduction in startle magnitude on prepulse+pulse trials, compared to the mean startle magnitude on pulse-alone trials over a specified portion of the test session; difference scores quantify PPI as the arithmetic difference between startle magnitude on pulse alone trials and prepulse+pulse trials (Ison and Hoffman 1983; Davis 1988; Mansbach et al. 1988; Davis et al. 1990). Both percent and difference scores have their appropriate uses, and can be utilized together to obtain a full assessment of PPI. It is important to note, however, that interventions that cause significant changes in pulse-alone startle magnitude offer a special challenge in interpreting changes in PPI, as they relate to inferences regarding changes in the startle-inhibiting effects of the prepulse (see accompanying manuscript; Swerdlow et al. 2001d).

Developmental course of PPI in humans

Ornitz and others have reported on a series of interesting studies of the developmental course of PPI in humans. Graham, Strock and Ziegler (1981) reported that infants show PPI, beginning at least by several months of age when long prepulse intervals and relatively weak prestimuli are used. Ornitz et al. (1986) examined PPI in 3-, 4-, 5-, and 8-year-old boys, and adult males. Compared to younger boys, the 8-year-olds (and adults) showed greater PPI when a 20 ms, 75 dB tone pip preceded the startling stimulus by 120 or 250 ms. Ornitz et al. also observed a maturational decrease in startle facilitation at longer continuous lead intervals. In a subsequent study, Ornitz et al. (1991) reported studying 4- to 8-year-old girls and young women, and found a pattern of PPI development that was similar to that found in boys (fairly mature levels of PPI at age 8), but also reported that sex differences in PPI were already evident by age 8, with boys showing greater levels of PPI than girls. The investigators concluded that one explanation of these data is that the brainstem structures that mediate PPI are probably not fully functional until ages 8–10 (Ornitz et al. 1991). These investigators have also suggested that differences in the development of mature levels of PPI in patients versus normal control groups might reflect developmental delays in brain circuitry that mediate PPI. While this type of "developmental" model generally portrays PPI development over the period of 4–8 years as a monotonic ascending function, it is certainly conceivable that in any individual, PPI undergoes both increases and decreases across development, from infancy to adulthood. Such changes might be expected, based on the differential maturation of sequential forebrain circuitry (e.g. descending serial striato-pallido-pontine GABAergic neurons) that might alternately increase or suppress PPI (see Swerdlow et al. 2001d, this issue). The neurobiology and pathological implications of developmental changes in PPI in humans may be studied in animal models. As described in accompanying papers (Geyer et al. 2001; Swerdlow et al. 2001d), animal studies suggest that pharmacological manipulations may be differentially effective, depending on whether or not PPI is fully "developed" (Martinez et al. 2000, 2001), and isolation rearing (Geyer et al. 1993) and early hippocampal lesions in rat pups (Lipska et al. 1995) can lead to later PPI abnormalities.

Effects of prepulses on perceived intensity of startle stimuli

There have been many hypotheses about the relationship between PPI and "information-protective" processes in the nervous system (Graham 1975; Braff et al. 1978; Braff and Geyer 1990; Swerdlow 1996). Most simply, in a prepulse+pulse trial with a 100 ms prepulse-to-pulse interval, the startling pulse is thought to "arrive" during a period of relatively diminished responsivity, a result of the brain's efforts to "protect" the information contained within the prepulse. If this is the case, then in the aftermath of a prepulse, it might be possible to quantify the inhibition of the perceived "intensity" of the startling stimulus. This inhibition of perceived intensity of a startling stimulus by a prepulse was first reported by Peak (1937), and has been reproduced and extended in a number of studies, using startle stimuli in tactile, acoustic, or electrocutaneous modalities (Cohen et al. 1981; Perlstein et

al. 1993; Blumenthal et al. 1996; Norris and Blumenthal 1996; Blumenthal et al. 2001). In general, PPI of perceived startle stimulus intensity is small (maximal values of approximately 15–25% reduction, depending on the experimental conditions) compared to PPI of startle reflex magnitude (which often is 100%). There are reasons to believe that these two different effects of prepulses (inhibition of perceived intensity and motor inhibition) may be regulated by overlapping but non-identical brain substrates (see Swerdlow et al. 2001d, in this issue).

Prepulse inhibition deficits in neuropsychiatrically disordered patients

Interest in PPI as a measure of sensorimotor gating in a neutral uninstructed paradigm has been stimulated by findings that disorders with known dysfunction in brain substrates that regulate PPI are accompanied by evidence of impaired cognitive, motor or sensorimotor inhibition. Deficient PPI is reported in patients with schizophrenia (e.g. Braff et al. 1978, 1992, 1999, 2001; Bolino et al. 1994; Kumari et al. 1999, 2000; Weike et al. 2000) and related non-medicated, non-psychotic schizotypal patients (Cadenhead et al. 1993), as well as patients with obsessive compulsive disorder (OCD) (Swerdlow et al. 1993a), Huntington's disease (HD) (Swerdlow et al. 1995c), nocturnal enuresis and attention deficit disorder (Ornitz et al. 1992), Tourette syndrome (Castellanos et al. 1996; Swerdlow et al. 2001b), blepharospasm (Gomez-Wong et al. 1998), non-epileptic seizures (Pouretemad et al. 1998) and, perhaps, post-traumatic stress disorder (PTSD) (Grillon et al. 1996). Strikingly, these disorders are all characterized symptomatically by a loss of gating in sensory, motor, or cognitive domains, and in some cases, by known or proposed abnormalities in the cortico-striato-pallido-pontine (CSPP) circuitry that modulates PPI. Importantly, PPI deficits are not unique to a single form of psychopathology, but fit into a rational picture of CSPP and related cortico-striato-pallido-thalamic (CSPT) dysfunction across multiple disorders (Swerdlow et al. 1992).

Schizophrenia spectrum disorders

PPI has been particularly valuable for studying the neurobiology of schizophrenia, because of the relevance of the gating "anatomy" to the pathophysiology of this disorder, and because deficits in gating of cognitive and sensory information are clinically important features of this disorder. While it is clear that schizophrenia patients are impaired in measures of sustained or "voluntary" attention (Callaway and Naghdi 1982), clinically and experimentally they also demonstrate an inability automatically to filter or "gate" irrelevant thoughts and sensory stimuli from intruding into conscious awareness (Venables 1960; McGhie and Chapman 1961; Braff et al. 1978). It is this automatic processing in the neutral, uninstructed paradigm that connects to animal model studies of PPI (see Swerdlow et al. 2001d and Geyer et al. 2001, this issue).

PPI deficits and correlated cognitive and symptomatic abnormalities have been reported in schizophrenia patients and individuals within the "schizophrenia spectrum" of disorders (Braff et al. 1978, 1992, 1999, 2001; Grillon et al. 1992; Cadenhead et al. 1993, 2000; Bolino et al. 1994; Karper et al. 1996; Perry and Braff 1996; Perry et al. 1998; Kumari et al. 1999, 2000; Parwani et al. 2000; Weike et al. 2000). Table 1 provides additional details of these PPI studies and deficits associated with disrupted PPI. These studies confirm that schizophrenia patients exhibit reduced PPI (usually on a percentage basis) independently of whether auditory, tactile, or electrocutaneous stimuli are used to elicit startle and PPI (Braff et al. 1978, 1992, 2001; Grillon et al. 1992; Bolino et al. 1994; Kumari et al. 1999, 2000; Weike et al. 2000). Furthermore, both intra-modal and cross-modal PPI has been found to be reduced in schizophrenia patients (Table 1; Braff et al. 1992). Thus, the sensorimotor gating deficits assessed by PPI in schizophrenia appear to generalize across modalities. The findings summarized in Table 1 also indicate that PPI deficits are found in schizophrenia when either continuous or discrete prepulses are used. Similar deficits in PPI are seen in schizotypal patients who are not grossly psychotic or receiving antipsychotic medications (Cadenhead et al. 1993), and in unaffected first-degree relatives of schizophrenia probands (Cadenhead et al. 2000). The finding that PPI is reduced in unaffected relatives of schizophrenia probands, compared to controls, makes PPI an important and valid candidate as an intermediate or endophenotypic marker in genetic studies (Braff and Freedman 2001).

Several findings address the issue of whether schizophrenia-related deficits accrue from gross psychosis or antipsychotic medications. First, preclinical studies, reviewed in this issue (Geyer et al. 2001), consistently demonstrate that antipsychotic medications either have no effect, or actually increase PPI in laboratory animals. In addition, no studies in infrahumans have identified significant reductions in PPI after acute or chronic treatment with antipsychotic medications. Second, non-medicated schizotypal personality disordered (SPD) patients show deficient PPI in auditory paradigms (Cadenhead et al. 1993). Third, Cadenhead et al. (2000) reported that clinically unaffected relatives of schizophrenia patients have PPI deficits, supporting the idea that neither medications nor gross psychosis accounts for schizophrenia-related PPI deficits.

Several crucially informative studies have investigated the relationship between PPI and cognitive deficits in schizophrenia. For example, PPI deficits correlate significantly with thought disorder (Perry and Braff 1994) and even more highly (r=–0.78) when both PPI and thought disorder are assessed in a single test session (Perry et al. 1999). Karper et al. (1996) reported that lower PPI is associated with greater distractibility in schizophrenia patients. PPI deficits are also observed in individuals who have an MMPI profile associated with specific neuropsy-

Table 1 PPI deficits in schizophrenia spectrum patients. All stimuli are white noise unless frequency in Hz is specified

Reference	Group and medications	PPI deficits compared to controls	Correlates of PPI	Eye	Background	Startle stimuli	Prepulse stimuli	ISI
Bolino et al. (1994)	Medicated (*n*=18)	PPI deficits	Not assessed	R and L	Unspecified	1 ms 3.7 mA or greater electrocutaneous stimulus	1 ms 0.92 mA electrocutaneous stimulus	30, 60, 120, 750, 2000
Braff et al. (1978)	Medicated (*n*=11), unmedicated (*n*=1)	PPI deficits	Not assessed	R	Unspecified	50 ms 104 dB	Continuous 71 dB 1000 Hz	0, 30, 60, 120, 240, 500, 2000
Braff et al. (1992)	Typical antipsychotics (*n*=26), unmedicated (*n*=1)	PPI deficits both with auditory and tactile startle stimuli	None significant	R	70 dB	40 ms 116 dB, 30 psi airpuffs	20 ms 85 dB	30, 60, 120
Braff et al. (1999)	Males only, typical and atypical (*n*=31), unmedicated (*n*=6)	PPI deficits	Global SAPS, global SANS, age	R	70 dB	40 ms 118 dB	20 ms 72, 74, 78 and 86 dB	60
Braff et al. (2001)	Typical antipsychotics (*n*=5), atypical antipsychotics (*n*=12), both (*n*=8)	PPI deficits	Not assessed	R and L	70 dB	40 ms 115 dB	Discrete (20 ms) 85 dB white noise or 1000 Hz Continuous 85 dB white noise or 1000 Hz	60
Cadenhead et al. (1993)	Schizotypal personality disorder (*n*=16), medicated (*n*=2), unmedicated (*n*=14)	PPI deficits with auditory startle stimuli, no deficits with tactile startle stimuli	Not assessed	R	70 dB	40 ms 116 dB, 30 psi airpuffs	20 ms 85 dB	30, 60, 120
Cadenhead et al. (2000)	Schizophrenia patients (*n*=23: typical antipsychotics *n*=9; atypical *n*=13; unmedicated *n*=1), family members (*n*=34: atypicals *n*=1; antidepressants *n*=4), schizotypal personality disorder (*n*=11:typical antipsychotics *n*=1; antidepressants *n*=1; mood stabilizers *n*=2)	PPI deficits in all three groups	Not assessed	R and L	70 dB	40 ms 115 dB	20 ms 86 dB	30, 120
Dawson et al. (1993)	Unmedicated (*n*=12), typical antipsychotics (*n*=3)	PPI deficits in attend to prepulse condition only	Not assessed	L	Unspecified	50 ms 100 dB	25 ms 70 dB 800 and 1200 Hz	60, 120, 240, 2000
Grillon et al. (1992)	Typical antipsychotics (*n*=12), unmedicated (*n*=2)	PPI deficits across all prepulse intensities	None significant	L	70 dB	40 ms 106 dB	20 ms 75, 80, 85 and 90 dB	120
Karper et al. (1996)	Medicated (*n*=28)	Not assessed	Distractibility	R	70 dB	40 ms 105 dB	40 ms 80 dB	120, 250, 1000, 2000
Kumari et al. (1999)	Clozapine (*n*=11), typical antipsychotics (*n*=9)	Normal PPI for clozapine group; PPI deficits in typical antipsychotic group	Not assessed	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Kumari et al. 2000	Typical antipsychotics (*n*=9), atypical antipsychotics (*n*=29)	PPI deficits in typical antipsychotic group only	Onset of illness	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120

Table 1 (continued)

Reference	Group and medications	PPI deficits compared to controls	Correlates of PPI	Eye	Background	Startle stimuli	Prepulse stimuli	ISI
Parwani et al. 2000	Outpatients (*n*=15: typicals, *n*=7; atypicals *n*=2; unmedicated *n*=1), acute inpatients (*n*=9: PRN neuroleptics)	PPI deficits	None significant	R	70 dB	40 ms 116 dB	20 ms 85 dB	30, 60, 120
Perry and Braff (1994)	Medicated (*n*=45), unmedicated (*n*=7)	Not assessed	Thought disorder	R	70 dB	40 ms 116 dB, 30 psi airpuffs	20 ms 85 dB	30, 60, 120
Perry et al. (1999)	Typical antipsychotics (*n*=13), atypical antipsychotics (*n*=8), unmedicated (*n*=1)	Not assessed	Thought disorder	R	70 dB	40 ms 118 dB	20 ms 78 dB	120
Perry et al. (2001)	Typical antipsychotics (*n*=3), atypical antipsychotics (*n*=11), unmedicated (*n*=17)	PPI deficits found in all three groups of patients	Not assessed	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Weike et al. (2000)	Typical antipsychotics (*n*=11), atypical antipsychotics (*n*=9), unmedicated (*n*=7)	PPI deficits in unmedicated group only	Positive syndrome (PANSS)	L	Unspecified	50 ms 105 dB	20 ms 85 dB 1000 Hz	30, 60, 120, 240

chological deficits (Swerdlow et al. 1995a), although the correlation of PPI deficits with a large number of neuropsychological tests has proven less than impressive (Swerdlow et al. 1995a). Other demographic and symptom measures associated with reduced PPI in schizophrenia include early age of onset (Kumari et al. 2000), and greater positive or negative symptoms (Braff et al. 1999). In both cases, however, there are conflicting reports in the literature (Perry and Braff 1994; Braff et al. 1999; Kumari et al. 1999), suggesting that some of these observed relationships may reflect characteristics peculiar to specific patient cohorts (e.g. restricted age or symptom range, stage of illness, and history of treatment), or experimental parameters. Indeed, despite the great weight of the literature supporting the occurrence and importance of PPI deficits in schizophrenia patients, there are two reports of a lack of PPI deficits in these patients, albeit both reports utilized complex paradigms and slightly different patient subgroups (Dawson et al. 1993; Ford et al. 1999). Thus, future studies will undoubtedly report attempts to reconcile a number of questions about the nature and extent of PPI deficits in schizophrenia spectrum patients (see below).

Obsessive compulsive disorder

Swerdlow et al. (1993a, 1997b) measured acoustic sensorimotor gating in acoustic startle in two samples of OCD patients and normal comparison subjects. Deficient PPI was reported in both samples in measures of right eyeblink startle, but as discussed above, in the one study that assessed left eyeblink measures, left eyeblink PPI did not differ significantly between OCD and control groups (Swerdlow et al. 1997b). In a different paradigm, Schall et al. (1996) also reported a small but statistically reliable attenuation of gating in OCD patients compared to normal subjects.

Tourette syndrome, enuresis, and attention deficit hyperactivity disorder in children

PPI deficits have also been reported in patients with Tourette's syndrome (TS). Castellanos et al. (1996) compared PPI in boys comorbid for attention deficit hyperactivity disorder (ADHD) and a tic disorder, with a group of well-screened normal comparison subjects, and with boys who had ADHD alone. The startle response was elicited utilizing supraorbital nerve electrical stimulation and PPI was assessed measuring the decrease in amplitude resulting from electric prestimuli just above sensory threshold. Boys comorbid for ADHD and tic disorder had significantly decreased PPI compared to normal controls, and compared to boys with ADHD alone. Previously, Smith and Lees (1989) reported abnormalities in electrocutaneous paired-pulse inhibition in TS subjects. It may ultimately be important to segregate neurobiological studies in TS based on the age

(child versus adult) of the subjects, because recent findings indicate that only approximately 50% of all childhood TS persists into adulthood (Leckman et al. 1999). Acoustic startle magnitude, latency and habituation are normal in adults with TS (Sachdev et al. 1997). Swerdlow et al. (1994) also found normal levels of PPI in adults with TS, but reduced PPI levels in TS children in a paradigm using auditory startle and prepulse stimuli, and more recently replicated and extended this finding to include deficits in TS children in a paradigm using unimodal tactile (air puff) startle and prepulse stimuli (Swerdlow et al. 2001b).

ADHD is a common comorbid condition in neurodevelopmental disorders other than TS. Ornitz et al. (1992) examined PPI in 43 boys with ADHD, 13 of whom had been diagnosed with enuresis, 17 age-matched enuretic boys and 42 age-matched normal control boys. Startle modulation was induced using 60 and 120 ms prestimulation intervals with a 4000 ms continuous tone. There was no effect of ADHD on startle modulation by prestimuli, but there was a significant effect of enuresis (reduced PPI, independent of ADHD). More recently, Ornitz et al. (1999) further evaluated the association of PPI deficits with enuresis and comorbid ADHD. In this study, 31% of the enuretic and 36% of the non-enuretic boys were diagnosed with ADHD. There was a significant association between enuresis and deficient PPI at the 120 ms prepulse interval, with boys who had enuresis and ADHD showing the greatest PPI deficit. This finding is consistent with that of Castellanos et al. (1996), in suggesting that PPI is not deficient in boys diagnosed with ADHD, who lack a comorbid disorder. This observation is also consistent with one preliminary report of PPI in adults with "pure" ADHD, who actually exhibited increased PPI, compared to normal control subjects (Adler et al. 1999).

Blepharospasm

Blepharospasm is a focal dystonia manifested by involuntary excessive blinking and squeezing of the eyes (Feiwell et al. 1999). Gomez-Wong et al. (1998) demonstrated impaired electrocutaneous PPI in patients with blepharospasm, compared to normal controls. At short lead intervals, comparable prepulse facilitation occurred in both groups, while PPI, observed with prepulse intervals between 50 and 200 ms, was reduced in over half of the patients. The investigators postulated that a sensory deficit might contribute to the maintenance of dystonic spasms by reducing the amount of physiological gating from peripheral nerve inputs. Certainly, the relationship between impaired PPI and symptoms in blepharospasm is not clear; it is indeed conceivable that both PPI deficits and symptoms in these patients arise from a common brain disturbance, but that different mechanisms are responsible for impaired inhibition of involuntary (startle-induced) eyeblinks versus impaired inhibition of voluntary eye blinks.

Temporal lobe epilepsy (with psychosis) and non-epileptic seizure disorder

In one published abstract, Morton et al. (1994) reported PPI deficits in patients with temporal lobe epilepsy (TLE) and psychosis compared to non-psychotic patients with TLE. Unfortunately, this observation has been difficult to assess critically and must be viewed as only a potential lead, because the full report of this study remains unpublished. Others (Pouretemad et al. 1998) reported PPI deficits in individuals with "non-epileptic seizures", which may constitute a variant of TLE. This latter observation suggests that psychosis per se is not a requirement for deficient PPI in seizure disorder patients, consistent with findings of PPI deficits in non-psychotic SPD patients (discussed above) and with recent preliminary evidence for reduced PPI in non-psychotic patients with bipolar affective disorder (Perry et al. 1999). As discussed in an accompanying paper (Swerdlow et al. 2001d, this issue), preclinical studies suggest that PPI in rats is impaired after manipulations of the temporal lobes, including electrical kindling of the amygdala (Koch and Ebert 1998) and chemical activation of the ventral hippocampus (Wan et al. 1996).

Post-traumatic stress disorder

An exaggerated startle response is one of the diagnostic criteria for post-traumatic stress disorder (PTSD) (APA 2000). Studies have quantified acoustic startle magnitude in combat veterans with PTSD (Butler et al. 1990; Grillon et al. 1996, 1998; Morgan et al. 1996), in children diagnosed with PTSD (Ornitz and Pynoos 1989), or in women diagnosed with PTSD following sexual assault (Morgan et al. 1997). Conflicting results have been published with reports of diminished (Ornitz and Pynoos 1989), normal (Grillon et al. 1996), and increased startle magnitude (Butler et al. 1990; Morgan et al. 1996; Grillon et al. 1998) and of normal (Butler et al. 1990; Grillon et al. 1998) and deficient PPI (Ornitz and Pynoos 1989; Grillon et al. 1996) in subjects with PTSD. Ornitz and Pynoos (1989) reported PPI deficits in six children diagnosed with PTSD compared to six normal control children, using 104 dB startling noise bursts and 75 dB(A) 1000 Hz tone prestimuli. Butler et al. (1990) compared 20 Vietnam veterans diagnosed with PTSD to 18 veterans with comparable combat experience but without PTSD, on an auditory and tactile startle paradigm. It was postulated that the PTSD-diagnosed veterans would exhibit larger startle magnitude and/or reduced startle thresholds, compared to matched controls. In support of the latter hypothesis, subjects diagnosed with PTSD had significantly reduced thresholds for the elicitation of acoustic startle (group differences at 95 and 100 dB(A)), but no differences in startle magnitudes with more intense acoustic or tactile (air puff) stimuli. Groups did not differ in the amount of unimodal (auditory) and cross-modal (tactile) PPI. Grillon et al. (1996) compared 21

unmedicated Vietnam veterans with PTSD to separate groups of civilian controls and Vietnam veterans. Startle stimuli consisted of 98 and 103 dB(A) SPL noise bursts of 40 ms duration; prestimuli were 30 ms, 70 dB(A) SPL noise bursts which preceded the startle stimuli by 120 ms. All groups exhibited similar startle magnitudes. The PTSD group exhibited reduced PPI relative to the civilian control group, but not relative to the veteran control group. More recently, Grillon et al. (1998) examined the effect of darkness on startle magnitude and PPI in Vietnam veterans with PTSD, compared to veterans without PTSD and civilian controls. In contrast to the earlier Grillon et al. (1996) study, the overall level of startle magnitude was higher in veterans with PTSD than in comparison groups, and percent PPI did not significantly differ between any of the groups. For all subjects, darkness increased startle magnitude and this facilitation was greater in the PTSD group. PPI was unaffected by darkness. Thus, the issue of whether PTSD patients (and which subgroups of these patients) have PPI deficits remains unresolved.

PTSD studies of PPI illustrate one point made above – conflicting results may be attributed to differences in the experimental parameters used. Butler et al. (1990) had a continuous background noise of 70 dB(A) while in the two Grillon et al. studies, there was no reported controlled background noise. The Butler et al. study also used much higher startle stimulus intensities and louder prepulses than did the other studies. All studies used an ISI of 120 ms. In the Ornitz and Pynoos study, the prepulse was a 1000 Hz tone, versus a burst of white noise in Butler et al. (1990). Finally, when comparison groups differ in the level of startle magnitude on pulse-alone trials, it is important to consider the potential impact of this difference on calculations of PPI. Startle magnitude was decreased, increased, and unchanged in PTSD subjects, across several different studies; conceivably, these different patterns of startle magnitude may have contributed to differences in the observed group patterns of PPI. Eventually, it will be crucially important to arrive at consensus paradigms for one or all of the disorders discussed in this section.

Pharmacological studies in human subjects

As an outgrowth of our knowledge of PPI deficits in patients with various neuropsychiatric disorders and in parallel with translational animal model studies (see Geyer et al. 2001; Swerdlow et al. 2001d, this issue), investigators have increasingly utilized psychopharmacological strategies in normal humans using a number of carefully selected compounds. This approach is still in its relatively early stages but has begun to show some promise for comparing drug effects across species and/or simulating neurochemical disturbances proposed to underlie specific disorders. For example, the logical first step in investigations of psychopharmacological challenges in humans, as in animals (Geyer et al. 1990), has been the utilization of dopamine agonists, psychotomimetics, and NMDA antagonists. Thus, much of the human literature has focused on PPI deficits in schizophrenia-spectrum patients, and the compounds cited above are all relevant to understanding these disorders. Recently, the utilization of real or even potentially psychotomimetic or neurotoxic agents in human research is being increasingly restricted for a number of reasons, including growing restrictions on challenge studies in schizophrenia and even prohibitions on administering compounds of greater than minimal risk to normal volunteer subjects (Davis et al. 1999). Although we will not address these ethical issues here in any detail, it is important to stress that there are many available challenge strategies that can be utilized safely. This section is organized according to the types of compounds used to elicit changes in PPI in normal human subjects.

Dopaminergic compounds

Across many preclinical studies, the activation of dopamine receptors by either indirect agonists, such as amphetamine, or direct agonists, such as apomorphine, leads to robust deficits in PPI (see Geyer et al. 2001, this issue). Similarly, in human volunteers, Abduljawad et al. (1998) found that the D_2 dopamine agonist bromocriptine significantly reduced PPI. This result was found in a study using 12 males in four sessions where subjects received oral doses of placebo, the D_2 receptor agonist (and probable D_1 receptor partial agonist) bromocriptine (1.25 mg), the D_2 receptor antagonist haloperidol (3 mg), and a combined treatment with the cited doses of bromocriptine and haloperidol in a balanced double-blind protocol. Two hours after ingestion of haloperidol or 90 min after ingestion of bromocriptine, a 30 min EMG recording from the orbicularis occuli muscle of the right eye was taken to assess PPI. As summarized in Table 2, the PPI test session used 115 dB(A) sound pulses to elicit startle and 75 and 85 dB(A) prepulses to elicit PPI. We will not report all the specific parameters in this section, but only report some of these variables to illustrate how the reader can cross-reference Table 2. We discuss parametric issues where they may account for discrepant or counter-intuitive patterns of results. In both prepulse intensity conditions, the prepulse-to-pulse interval was 120 ms. The authors found that the baseline startle response was not altered by any of the pharmacological treatments. In all conditions, PPI was observed to be appropriately dependent upon the prepulse intensity. In both prepulse conditions, bromocriptine robustly reduced PPI. Somewhat paradoxically, the dopamine antagonist haloperidol also elicited a much smaller, albeit statistically significant, decrement in PPI. Subsequently, the same group confirmed similar findings with bromocriptine but failed to replicate the small effect of haloperidol on PPI (Abduljawad et al. 1999). Hence, the apparent effect of haloperidol by itself on PPI in humans does not appear to be reliable. In both reports, however, haloperidol was effective in antagonizing the PPI-disruptive ef-

Table 2 Effect of different drugs on PPI in normal human subjects (the reader is referred to the text for important details). All stimuli are white noise unless frequency in Hz is specified

Drug	Effect on PPI	Reference	Eye	Background	Startle stimuli	Prepulse stimuli	ISI (ms)
Ketamine							
Ketamine 0.3 mg/kg IV	No effect	Van Berckel et al. (1998)	R	70 dB	30 ms 108 dB	30 ms 87 dB	120
Ketamine 0.5 mg/kg	Increased PPI at 30 ms	Duncan et al. (2001)	R	70 dB	40 ms 116 dB 1000 Hz	20 ms 85 dB 1000 Hz	30, 60, 120
Dopaminergics							
Bromocriptine 1.25 mg	Disrupted PPI	Abduljawad et al. (1998)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120
Haloperidol 3 mg	Disrupted PPI	Abduljawad et al. (1998)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120
Bromocriptine 1.25 mg plus haloperidol 3 mg	Effect of bromocriptine reversed	Abduljawad et al. (1998)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120
Bromocriptine 1.25 mg	Disrupted PPI	Abduljawad et al. (1999)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120
Haloperidol 3 mg	No effect	Abduljawad et al. (1999)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120
Bromocriptine 1.25 mg plus Haloperidol 3 mg	Effect of bromocriptine reversed	Abduljawad et al. (1999)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120
Haloperidol 2 mg	No effect	Kumari et al. (1998)	R	70 dB	40 ms 116 dB	20 ms 79 dB	30, 60, 120
Haloperidol 5 mg	Disrupted PPI in smokers	Kumari et al. (1998)	R	70 dB	40 ms 116 dB	20 ms 85 dB	30, 60, 120
Haloperidol 1.4 mg IV	No effect	Liechti et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 86 dB	30, 60, 120, 240, 2000
d-Amphetamine 5 mg	Disrupted PPI in smokers	Kumari et al. (1998)	R	70 dB	40 ms 116 dB	20 ms 85 dB	30, 60, 120
d-Amphetamine 20 mg	Disrupted PPI in non-smokers	Hutchison and Swift (1999)	R	54 dB	50 ms 105 dB	30 ms 58 dB 800 Hz	120
Cocaine withdrawal	Increased PPI at 75 dB	Efferen et al. (2000)	R	70 dB	40 ms 116 dB 1000 Hz	20 ms 75, 80 and 85 dB 1000 Hz	100
Nicotine							
Cigarette smoking	Increased PPI	Kumari et al. (1996)	R	70 dB	40 ms 116 dB	20 ms 85 dB	30, 60, 120
6 µg/kg (subcutaneous)	No effect	Kumari et al. (1997)	R	75 dB	40 ms 116 dB	30 ms 84 dB	30, 60, 120
12 µg/kg (subcutaneous)	Increased PPI	Kumari et al. (1997)	R	75 dB	40 ms 116 dB	30 ms 84 dB	30, 60, 120
Cigarette smoking	Increased PPI	Della Casa et al. (1998)	R	65 dB	40 ms 108 dB	20 ms 80 dB	30, 60, 120
Caffeine							
Caffeine 2 and 4 mg/kg	No effect	Flaten and Elden (1999)	L	Unspecified	50 ms 100 dB	Continuous 45 dB 1000 Hz (p. 323) or 200 Hz (p. 324)	30, 60, 90, 120, 150, 180, 210, 410
Caffeine 200 mg	No effect overall; increased PPI in subjects in caffeine withdrawal	Swerdlow et al. (2000a)	R and L	70 dB	40 ms 118 dB	20 ms 86 dB	100
Caffeine 200 mg	No effect	Swerdlow et al. (2000a)	R and L	70 dB	40 ms 40 PSI airpuff	20 ms 86 dB	40
Anxiolytics							
Clonidine 200 µg	No effect	Abduljawad et al. (1997)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120
Diazepam 10 mg	No effect	Abduljawad et al. (1997)	R	70 dB 1000 Hz	40 ms 115 dB 1000 Hz	40 ms 75 and 85 dB 1000 Hz	120

Table 2 (continued)

Drug	Effect on PPI	Reference	Eye	Background	Startle stimuli	Prepulse stimuli	ISI (ms)
Ethanol (3.19 mg/kg males, 2.55 mg/kg females)	Disrupted PPI in those with low baseline PPI; increased PPI in those with high baseline PPI	Hutchison et al. (1997)	R	Unspecified	50 ms 105 dB	30 ms 58 dB 800 Hz	120
Ethanol 0.85 g/kg	Reduced startle; Confounding PPI measure	Grillon et al. (1994)	L	70 dB	40 ms 108 dB	30 ms 85 dB	120
Midazolam 0.02–0.14 mg/kg	Reduced startle; Confounding PPI measure	Schachinger et al. (1999)	R	Unspecified	50 ms 95 dB	50 ms 65 dB 800 Hz	120
Serotonergics							
MDMA 1.7 mg/kg	Increased PPI	Vollenweider et al. (1999)	R	70 dB	40 ms 115 dB	20 ms 78 and 86 dB	30, 120
MDMA 1.5 mg/kg	Increased PPI	Liechti et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 86 dB	30, 60, 120, 240, 2000
MDMA after citalopram (40 mg IV)	Attenuated MDMA increase in PPI	Liechti et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 86 dB	30, 60, 120, 240, 2000
MDMA after haloperidol (1.4 mg IV)	No effect on MDMA increase in PPI	Liechti et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 86 dB	30, 60, 120, 240, 2000
MDMA after ketanserin (50 mg PO)	No effect on MDMA increase in PPI	Liechti et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 86 dB	30, 60, 120, 240, 2000
Citalopram 40 mg IV	No effect	Liechti et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 86 dB	30, 60, 120, 240, 2000
Ketanserin 50 mg PO	No effect	Liechti et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 86 dB	30, 60, 120, 240, 2000
Tryptophan depletion	Disrupted PPI	Phillips et al. (2000a)	R	70 dB 1 kHz	40 ms 115 dB 1 kHz	40 ms 85 dB 1 kHz	120
Psilocybin 0.2 mg/kg	Increased PPI	Gouzoulis-Mayfrank et al. (1998)	R	70 dB	20 ms 115 dB	20 ms 74, 78 and 86 dB	100
Anticholinergics							
Procyclidine 10 mg	No effect	Kumari et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Procyclidine 15 mg	Disrupted PPI	Kumari et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Antidepressants							
Amitryptiline 100 mg	No effect on PPI; reduced startle amplitude	Phillips et al. (2000b)	R	70 dB 1 kHz	40 ms 115 dB 1 kHz	40 ms 85 dB 1 kHz	120
Fluvoxamine 100 mg	No effect	Phillips et al. (2000b)	R	70 dB 1 kHz	40 ms 115 dB 1 kHz	40 ms 85 dB 1 kHz	120
Reboxetine 4 mg	No effect	Phillips et al. (2000b)	R	70 dB 1 kHz	40 ms 115 dB 1 kHz	40 ms 85 dB 1 kHz	120

fects of bromocriptine, confirming the similar results found in animals (see Geyer et al. 2001, this issue). Neither bromocriptine nor haloperidol produced self-rated changes in alertness, physiological finger tremor, systolic or diastolic blood pressure changes, or salivation. Also, as expected, bromocriptine significantly suppressed and haloperidol elevated serum prolactin levels. Furthermore, prolactin was not changed when both drugs were given in combination. Thus, it appears that, in healthy humans, the D_2 dopamine agonist bromocriptine produces a reduction in PPI that can be blocked by co-administration of the D_2 antagonist haloperidol.

The effects of dopamine agonists on PPI in humans have been further explicated in a study of the indirect dopamine agonist amphetamine, which reliably reduces PPI in rodents (see Geyer et al. 2001, this issue). Specifically, Hutchison and Swift (1999) reported that a 20 mg oral dose of *d*-amphetamine disrupted PPI in normal (non-smoking) human subjects. Both male and female (n=18 each) subjects were tested at 60, 90, and 120 min after drug ingestion in a brief repeatable PPI test using a single prepulse condition (see Table 2). In keeping with the rather weak prepulse stimulus used [58 dB(A) tone against a background of 54 dB(A) white noise], only low levels of PPI ranging from 17 to 30% were observed. As predicted from the rodent studies, *d*-amphetamine significantly reduced PPI, although only at the 90-min post-drug test. In contrast, subjective measures of the effects of amphetamine were affected at all time-points and heart rate was elevated at both the 90- and 120-min time-points. No gender differences were observed in these low levels of PPI, and gender did not interact with the effect of amphetamine on PPI. Hutchison et al. (1999) subsequently reported that the individuals who scored highest on the Novelty Seeking scale of the Tri-Dimensional Personality Questionnaire were most sensitive to the PPI-disruptive effects of *d*-amphetamine. Finally, Kumari et al. (1998) reported that both amphetamine (5 mg) and haloperidol (5 mg) significantly reduced PPI, but only in the subgroup of normal subjects who were smokers. It will be important for researchers to expand upon this interesting approach to understanding trait-related (e.g. novelty seeking) and other contributions (e.g. smoking) to the effects of drugs on measures such as PPI. Further studies with additional doses and stimulus parameters will be useful to clarify the relationships between changes in PPI and other effects of amphetamine, as well as the specific conditions and populations in which the effects of amphetamine on PPI are most robust.

The results of these four studies provide evidence for the involvement of D2 dopamine receptors in the modulation of PPI in humans. This is an excellent example of a "translational" approach, because it had already been shown that PPI in rats is reliably disrupted by both direct and indirect dopamine agonists, and this disruption can be reversed by neuroleptics (see Geyer et al. 2001, this issue). Further supporting the cross-species consistencies in these findings is the fact that the doses of dopamine agonists and antagonists that modified PPI in both humans and rats did so without causing concomitant changes in startle magnitude (Mansbach et al. 1988).

Ketamine

Van Berckel et al. (1998) provided the first report of the effects of a low dose of the NMDA antagonist ketamine on sensory gating in healthy human subjects. Given the recent interest in the role of glutamatergic *N*-methyl-*d*-aspartate receptors (NMDA) in animal studies of PPI (see Geyer et al. 2001, this issue), these authors attempted to translate animal model data into the human realm. They noted that data on NMDA antagonist effects on PPI in human subjects are lacking despite their potential importance for understanding sensorimotor gating deficits in conditions such as schizophrenia. Accordingly, the authors tested the effects of the NMDA antagonist, ketamine (0.3 mg/kg) on PPI in 18 healthy male volunteers. Ketamine was administered intravenously (IV) via a subacute loading dose, which was followed by a continuous infusion in an attempt to create a steady state. The rather low dose of 0.3 mg/kg IV that was used induced a small increase in Brief Psychiatric Rating Scale (BPRS) Total Scores, as well as the BPRS sub-scales of thought disorder and withdrawal/retardation. As predicted, ketamine also induced increases in cortisol levels, systolic and diastolic blood pressure, and heart rate, indicating that the chosen dose was effective at least for these dependent measures. The authors observed no deficits in PPI (nor any deficits in the cerebral event related potential paradigm of P50 suppression), and suggested that the dose of ketamine used in this study might have been too low to produce significant effects on PPI. The authors noted that higher doses of ketamine might be difficult to use in humans, and concluded that future studies should use the more specific enantiomer, S-ketamine, in order to better evaluate the involvement of NMDA receptors in these neurophysiological processes.

In keeping with the suggestion of Van Berckel et al. (1998), a recent report by Duncan et al. (2001) examined the effects of a higher dose of ketamine on PPI in 16 healthy male subjects using a double-blind crossover design. Surprisingly, however, this higher dose of ketamine still did not decrease PPI, as was expected from the animal studies. Instead, ketamine produced a slight, but significant increase in PPI that was limited to the first block of the test session and the condition in which the prepulse-to-pulse interval was 30 ms. In comparison with the study of Van Berckel et al. (1998), the higher dose of ketamine used by Duncan et al. (2001) 0.5 mg/kg IV over 60 min versus 0.3 mg/kg IV over 135 min) clearly produced qualitatively similar but quantitatively larger effects on measures such as the BPRS total, thought disorder, and withdrawal/retardation scores. As summarized in Table 2, the other major difference between these two studies was that the Duncan et al. study included different prepulse-to-pulse intervals, ranging from 30 to 120 ms, whereas the Van Berckel et al. study used only

the 120-ms interval. Thus, with the 120-ms interval, neither study observed any significant change in PPI.

The only significant alteration in PPI observed by Duncan et al. was the increase in PPI with a relatively brief ISI. This finding is surprising because it is opposite to what was predicted on the basis of either the PPI-disruptive effects of ketamine and other NMDA antagonists PPI in rats (see Geyer et al. 2001, this issue) or the deficits in PPI reported in patients with schizophrenia (see above). In both of these contexts, decreases rather than increases in PPI are found with prepulse-to-pulse intervals ranging from 30 to 120 ms. In rats, the effects of ketamine on PPI are reported to be particularly sensitive to factors involving pharmacokinetics and stimulus parameters (Mansbach and Geyer 1991); indeed, the initial report of PPI deficits after NMDA antagonists in rats suggested that ketamine was ineffective in paradigms in which the non-competitive NMDA antagonist PCP was effective (Mansbach and Geyer 1989). Nevertheless, with the short prepulse-to-pulse intervals at which ketamine appears to increase PPI in humans, ketamine not only blocks PPI, but even produces prepulse facilitation of startle in rats (i.e. larger startle magnitude on prepulse+pulse trials, compared to pulse alone trials; Mansbach and Geyer 1991). Thus, there appears to be no precedent in the animal literature for an increase in PPI associated with the administration of an NMDA antagonist.

The disparity between the PPI-increasing effects of ketamine in healthy volunteers and the PPI deficits seen in schizophrenia patients might be viewed to be inconsistent with the idea that ketamine (and perhaps other NMDA antagonists) provide drug-induced model psychoses. Perhaps a more discerning interpretation of this finding is that, under specific conditions, NMDA receptor blockade in normal subjects may not provide a useful model for the neurochemical basis for deficient sensorimotor gating in schizophrenia. Clearly, ketamine and other NMDA antagonists appear to produce other sensory, cognitive, and behavioral changes in normal subjects that model clinical symptoms in schizophrenia patients. Duncan et al. (2001) noted that the clinical effects produced by ketamine in their study included robust increases in dissociative and negative symptoms. Conceptual disorganization has also been reported with sub-anesthetic doses of ketamine (Malhotra et al. 1996; Breier et al. 1997). The strongest correlation of PPI deficits with symptoms in schizophrenia patients is with thought disorder, a reflection of conceptual disorganization (Perry and Braff 1994; Perry et al. 1999). Nevertheless, the deficits in PPI seen in schizophrenia patients are not specifically correlated with negative rather than positive symptoms (Braff et al. 1999).

Certainly, this single report of a small increase in PPI produced by ketamine in the 30 ms condition cannot be viewed as disproving the hypo-glutamate hypothesis of at least some of the group of schizophrenia disordered patients. First, PPI deficits have not been considered to provide a model of the entire schizophrenia syndrome, but only of the sensorimotor gating deficits characteristic of many schizophrenic patients. Second, further parametric studies with ketamine in humans might still reveal conditions in which deficits in PPI are observed. Indeed, preliminary studies of the more selective (with regard to the PCP binding site associated with the NMDA receptor complex) S-enantiomer of ketamine indicate that some decreases in PPI are observed, depending upon the specific stimulus parameters used to elicit PPI (F. Vollenweider, personal communication). Third, in general, drug-induced model psychoses appear to have greater relevance to the incipient stages of schizophrenia than to the chronic stages of the illness (Gouzoulis-Mayfrank et al. 1998). To date, no reports have focussed on PPI in first-break schizophrenia patients. Fourth, the effects of ketamine in this model may not be fully representative of the effects of other NMDA antagonists. While ethical considerations preclude the use of PCP in studies of human PPI, Linn and Javitt (2001) recently reported that PCP disrupts PPI in infra-human primates, but has no significant effect on pulse-alone startle reflex magnitude. Additional studies of the effects of NMDA antagonists on PPI are needed to clarify the relationship between the effects of these drugs on PPI in healthy volunteers and the abnormalities in PPI observed in some schizophrenic patients. Informative avenues of investigation might include the use of different NMDA antagonists, more extensive dose ranges, and non-human primates.

Nicotine

A number of studies have examined the effect of nicotine and/or cigarette smoking on PPI. Part of the motivation for assessing the effects of nicotine on PPI in human subjects is the rather extensive literature on nicotinic effects in humans on a related measure of inhibition, the suppression of the P50 event-related-potential (ERP). In addition, some studies in rats indicate that PPI is increased by nicotine administration (Acri et al. 1994; Curzon et al. 1994). Another reason for examining nicotine effects is that anecdotal reports (which are admittedly unreliable) and more theoretical formulations have been proffered that link the high level of smoking in schizophrenia patients to a potential “naturalistic” attempt to normalize sensorimotor (and perhaps other) deficits in this population (Forchuk et al. 1997; Dalack et al. 1998; Markou et al. 1998). In this context, Kumari et al. (1996) first assessed cigarette smoking on PPI in healthy male smokers who were deprived of cigarettes overnight. Cigarette smoking in this group increased PPI compared to the smoking-deprived condition. Similarly, DellaCasa et al. (1998) compared non-smokers, deprived smokers, and smokers who smoked during the test session after deprivation or after ad lib smoking. They also found that smoking during the startle session increased PPI but did not affect startle magnitude or habituation. In this study, significant gender effects were noted; in men, ad lib smoking resulted in increased PPI compared to non-smokers while, in women, deprivation appeared to decrease PPI and smoking restored PPI to the level of non-

smokers. Kumari et al. (1997) next assessed the effect of acute nicotine (6 and 12 µg/kg delivered subcutaneously) on PPI in healthy male non-smokers. The higher dose of nicotine increased PPI significantly when percent scores were used, but not when absolute difference scores were used. Thus, although nicotine had no significant effect on startle magnitude, the disparity between the percent and difference scores prompts some caution in drawing firm conclusions from these data. Cumulatively, these results were interpreted to provide some support for the previous findings indicating that PPI is increased by cigarette smoking in overnight-deprived smokers, and more generally, for the notion that nicotinic receptor stimulation increases sensorimotor gating. Because of the rapid desensitization and sensitization of nicotinic receptors that are associated with nicotine administration and withdrawal, the physiological bases of these results are quite complicated and difficult to interpret. Nevertheless, Kumari et al. (1997) concluded that these findings indicate that previously observed effects of smoking on percent PPI in smoking-deprived subjects were not attributable to the reversal of a deficit that had been induced by smoking withdrawal, but instead represent a direct pharmacological action of nicotine itself.

Overall, the results of these studies in humans appear to be consistent with related reports of increased PPI induced by acutely administered nicotine in experimental animals (see Geyer et al. 2001, this issue). Other manipulations of cholinergic systems have seldom been studied in either rodents or humans. One exception listed in Table 2 is that the anticholinergic procyclidine has been found to disrupt PPI in humans (Kumari et al. 2001), which appears to be consistent with related studies in rats (Jones and Shannon 2000). As noted by Kumari et al. (1997), nicotine has been found to influence the dopaminergic system (e.g. Clark et al. 1984; Gray et al. 1994) as well as the cholinergic system. Both of these neural substrates might well modulate PPI, based on animal model data (see Geyer et al. 2001; Swerdlow et al. 2001d, this issue). Thus, because the modulation of PPI by nicotine may occur by dopaminergic, cholinergic, or other mechanisms, the authors concluded that their study could not be interpreted mechanistically; at a "functional" level, they suggested that the effect of nicotine in increasing PPI might relate to its attention/cognitive facilitating properties (Jones et al. 1992). These properties have been repeatedly observed in human subjects and might be related to the fact that PPI deficits correlate with cognitive and attentional abnormalities (Braff et al. 1992; Perry and Braff 1994; Karper et al. 1995; Swerdlow et al. 1995a).

Caffeine

Caffeine is a non-selective adenosine antagonist (Fredholm et al. 1994) and one of the most widely used psychoactive substances in man. In rats, caffeine (10 mg/kg) does not have significant effects on PPI, but it decreases startle amplitude (Bakshi et al. 1995). In humans, caffeine has been reported to delay reflex habituation, while having no significant effects on initial startle amplitude (Schicatano and Blumenthal 1994, 1995). Flaten and Elden (1999) first described a lack of effect of caffeine on startle magnitude or PPI in relatively heavy caffeine drinkers (mean=3.1 cups per day; minimum=2 cups per day). In a related study, Swerdlow et al. (2000a) assessed startle measures in adult male subjects 3 h after oral administration of caffeine (placebo or 200 mg; double-blind design). Subjects ranged from very low to very high caffeine users, and were tested either after a period of abstinence from normal caffeine use, or without such an abstinence period. Consistent with previous reports, caffeine increased alertness, caused mild autonomic activation, diminished startle habituation, and tended to reduce startle magnitude, but had no significant effects on PPI. Caffeine withdrawal was associated with marked psychological and somatic discomfort. A major implication of the findings of both Swerdlow et al. (2000a) and Flaten and Elden (1999) is that the PPI-disruptive effects of other drugs described in this review cannot be explained by generalized psychological or somatic effects; for example, the PPI-disruptive effects of amphetamine (Hutchison et al. 1999) cannot be explained simply on the basis of its effects on arousal (because caffeine increased arousal but did not disrupt PPI), and the PPI-disruptive effects of the DA agonists bromocriptine (Abduljawad et al. 1998) or apomorphine (Morton et al. 1995) cannot simply be explained by a drug-induced nausea or malaise, because caffeine withdrawal in the Swerdlow et al. (2000a) study was accompanied by elevated self-ratings of "sick" and "queasy", but not by changes in PPI.

The Swerdlow et al. (2000a) study included individuals whose normal caffeine intake was minimal (<100 mg/day), and who were thus least likely to experience withdrawal symptoms. In these individuals, neither caffeine nor placebo caused any change in PPI compared to "baseline" (no drug) levels. However, when all subjects were considered, there were clear interactions of caffeine, level of normal caffeine use, and state of caffeine withdrawal in measures of somatic symptoms, alertness, and change from "basal" levels of PPI. Specifically, caffeine increased PPI among high caffeine drinkers in withdrawal, but decreased PPI among high caffeine drinkers who were not in withdrawal, due to ad lib caffeine intake. Because caffeine consumption is widespread in many cultures, human subjects who are caffeine users can be in any one of several states of caffeine "intoxication" or withdrawal when they are tested for levels of PPI. The potential importance of caffeine withdrawal to drug effects on PPI is perhaps most applicable in studies that assess PPI in acutely hospitalized psychiatric patients, who are frequently not allowed caffeinated beverages during inpatient treatment. Most conservatively, the findings from Swerdlow et al. (2000a) suggest that comparison groups should be matched for caffeine use and withdrawal states. Finally, the findings of Swerdlow et al. (2000a) provide a clear example of the

difficulties of translational studies of PPI, in which findings from near-identical drug-naive rodents are extrapolated to findings in human populations in whom drug use (e.g. caffeine, theophylline, nicotine) is ubiquitous, and in whom drug levels and withdrawal states at the time of testing are both variable and difficult to assess.

Sedative/anxiolytic/antidepressant drugs

The effects of sedative, anxiolytic, and antidepressant drugs on PPI have been much more extensively examined in animals compared to humans, although not as extensively as their effects on acoustic startle magnitudes. In general, these drugs appear to have minimal effects on PPI in animals (see Geyer et al. 2001, this issue). In humans, Abduljawad et al. (1997) assessed the effects of clonidine and diazepam on startle and PPI in normal male volunteers. Subjects were tested in a within-subject design in which they received oral doses of placebo, 10 mg diazepam, and 0.2 mg clonidine in a balanced double-blind protocol. Using stimulus parameters summarized in Table 2, EMG recordings from the right eye were obtained 2 h post-ingestion of clonidine and 1 h after the ingestion of diazepam, based on considerations of absorption and maximal CNS effects of these two different compounds. Although both drugs dramatically reduced the magnitude of startle responses, neither drug significantly altered PPI calculated as a percent score. In addition, both drugs reduced self-rated alertness, and clonidine specifically reduced systolic blood pressure and salivation. Similarly, Schächinger et al. (1999) reported dramatic and dose-related decreases in acoustic startle after the administration of IV midazolam in human subjects. Although these authors also concluded that PPI was decreased as well, this result was likely due to a floor effect associated with the profound reduction in startle magnitude rather than an effect on PPI per se. In a related study of a CNS depressant, Grillon et al. (1994) reported that ethanol decreased startle responses to such an extent that PPI could not be assessed reliably. In another study of the effects of acute alcohol administration (Hutchison et al. 1997), startle reactivity was also reduced, but not so markedly that PPI could not be assessed. Surprisingly, this study indicated that ethanol reduced PPI in subjects who exhibited low levels of PPI at baseline but increased PPI in subjects who exhibited high levels of PPI at baseline. Overall, these studies suggest that anxiolytic drugs given in doses that can suppress startle magnitude itself have no consistent effect on PPI, which is consistent with the similar studies in laboratory animals (see Geyer et al. 2001, this issue). These results also support the hypothesis that the regulation of startle magnitude itself is separable from significant effects on the PPI modulatory circuitry, and provide at least indirect support for the differential neural substrates of these two phenomena. A variety of antidepressant drugs have been found to have no clear effects on PPI in either humans or animals. As summarized in Table 2, representative antidepressants from different subclasses, including tricyclics, serotonin-selective reuptake inhibitors, and norepinephrine-selective uptake inhibitors, have been examined in humans. None of these antidepressants altered PPI even at doses that had significant effects on startle reactivity in some cases or that blocked the effects of MDMA in other cases (Liechti et al. 2001; Phillips et al. 2001b).

Psilocybin

Gouzoulis-Mayfrank et al. (1998) assessed PPI in normal subjects after administration of the serotonergic hallucinogen, psilocybin, a mixed 5-HT-1 and 5-HT-2 direct agonist that induces a full range of positive psychotic symptoms (e.g. hallucinations, delusions) as well as confusional states. Psilocybin-induced symptoms thereby model some features of the incipient stages of some forms of schizophrenia. In a double-blind controlled study (placebo versus psilocybin, 0.2 mg/kg), subjects were invariably able to detect which drug condition they were in. Thus, as with the majority of these pharmacological studies, the study was partially lacking in terms of "blindedness". Still, about 1 h post-drug ingestion (when psychotic-like symptoms emerged), subjects were tested in a startle paradigm that included a 70 dB background, a 115-dB startling stimulus and prepulses of 4, 8 and 16 dB above background. In contrast to expectations based on the use of psilocybin in a drug-induced model psychosis, PPI was increased slightly in the 8 dB condition, rather than decreased as in schizophrenia. The authors speculated that the dose of psilocybin used might have induced a mild pre-psychotic state with a "compensatory" increase in PPI. Because other hallucinogenic serotonin agonists, such as 2,5-dimethoxy-4-iodoamphetamine (DOI), disrupt PPI in rats (see Geyer et al. 2001, this issue), this finding with psilocybin appears to represent a difference between drug effects on PPI in rats versus humans. Psilocybin, however, does not appear to disrupt PPI in rats reliably (Krebs-Thomson and Geyer, unpublished observations), perhaps because it is less selective as a serotonin agonist relative to DOI. As discussed elsewhere (Geyer et al. 2001, this issue), 5-HT_{1A} agonists increase PPI in mice despite the fact that they decrease PPI in rats. Thus, the 5-HT_{1A} agonist actions of psilocybin, which are not shared by DOI, may be responsible for the increased PPI observed in human subjects by Gouzoulis-Mayfrank et al. (1998). Only more extensive experiments using more selective pharmacological tools will resolve this question.

MDMA ("Ecstasy")

As reviewed elsewhere (Geyer et al. 2001, this issue), PPI in rats is disrupted by MDMA, fenfluramine, and other indirect serotonin agonists, i.e. drugs that act by inducing the release of presynaptic serotonin. Based on

these observations, Vollenweider et al. (1999) directly compared the effects of MDMA in rats and normal human volunteers in a PPI paradigm that was designed to be as identical as possible in the two species (see Table 2). In humans, a quantity estimated as a "typical" recreational dose of MDMA (1.7 mg/kg) was administered orally. In rats, a wide range of different doses (1.7–17.0 mg/kg) was administered by systemic injection. PPI testing was then conducted at the time of peak drug effects in each species. Despite these explicit efforts to conduct equivalent studies across species, opposite effects on PPI were observed. Thus, MDMA dose-dependently reduced PPI in rats, as expected from previous studies, and increased PPI in humans. In both species, the effects of MDMA on PPI were seen with a prepulse-to-pulse interval of 120 ms but not with an interval of 30 ms. Because the effects on PPI observed in each species were confirmed using both percent and difference scores, the PPI measures were not confounded by drug-induced changes in startle magnitude (which were non-significant in rats and only slightly increased in humans). Thus, the authors speculated that there might be a species-specific difference in the mechanism of action of MDMA or in the behavioral expression of a similar pharmacological effect, or both.

In rats, the primary mechanism of action of MDMA responsible for its effects on PPI and most other behaviors has been demonstrated to involve the release of presynaptic serotonin, acting in turn upon the multiple subtypes of post-synaptic serotonin receptors (Geyer and Callaway 1994). The major evidence for this mechanism is that serotonin reuptake blockers, such as fluoxetine or citalopram, prevent both the MDMA-induced release of serotonin and the behavioral effects of MDMA, as reviewed elsewhere (Geyer et al. 2001, this issue). Hence, a subsequent study by Vollenweider's group (Liechti et al. 2001) tested the hypothesis that the MDMA-induced increase in PPI in humans is attributable to the same mechanism of serotonin release as is the MDMA-induced decrease in PPI in rats. In keeping with published rat studies, double-blind placebo-controlled studies compared vehicle with 1.5 mg/kg MDMA after pretreatment with: (1) the highly selective serotonin uptake inhibitor citalopram (40 mg IV) in 16 subjects, (2) the dopamine D_2 antagonist haloperidol (1.4 mg IV) in 14 subjects, or (3) the 5-HT2 antagonist ketanserin (50 mg PO) in 14 subjects. As in the Vollenweider et al. (1999) study, MDMA by itself increased PPI when prepulse-to-pulse intervals of 60, 120, or 240 ms (but not 30 ms or 240+ ms) were used. By themselves, citalopram, haloperidol, and ketanserin had no significant effect on PPI. As predicted from the animal studies, citalopram pretreatment prevented the MDMA-induced increase in PPI in humans, while the pretreatments with haloperidol or ketanserin were ineffective. The failure of the latter two pretreatments is also consistent with studies in rats. Based on the rat literature, haloperidol would be expected to antagonize the effects of the dopamine releaser amphetamine (see above for human studies) and ketanserin would be expected to block the effects of a 5-HT_2-specific hallucinogen, such as DOI, but neither would be expected to block the effects of MDMA on PPI (see Geyer et al. 2001, this issue). Thus, it appears that the opposite effects of MDMA on PPI in rats versus humans are due to the same primary mechanism, that is, the release of presynaptic serotonin. This conclusion suggests that there is a species difference in the behavioral expression of the serotonin released by MDMA. Liechti et al. (2001) offer the testable hypothesis that this difference involves species-specific differences in the functions of 5-HT_{1A} receptors, in part because the effects of 5-HT_{1A} agonists on PPI are opposite in rats versus mice (Dulawa et al. 2000a). Hence, the recent studies of PPI effects in mice would predict that the serotonin released by MDMA in humans could act upon post-synaptic 5-HT_{1A} receptors and thereby increase PPI. Indeed, in knockout mice lacking 5-HT_{1B} receptors, which normally disrupt PPI when activated in mice, MDMA actually increases PPI as it does in humans (Dulawa et al. 2000b). Such an explanation of the species differences in the effects of MDMA on PPI would be consistent with the speculation that the increase in PPI produced by psilocybin in humans is due to its 5-HT_{1A} agonist actions. Future studies could test this hypothesis by examining the effects of selective 5-HT_{1A} agonists on PPI in humans or the effects of 5-HT_{1A} antagonists on the PPI-increasing effects of MDMA or psilocybin in humans.

Antipsychotic medications in schizophrenia patients

As summarized in Table 3, two studies have claimed that atypical antipsychotic medication "normalizes" PPI in schizophrenia patients (Kumari et al. 2000; Weike et al. 2000), but this conclusion was not fully supported in a third report (Perry et al. 2001). It is difficult to interpret the full implications of the two "positive" reports, because they were both based on between-subject comparisons. Thus, unmedicated schizophrenia patients (Weike et al. 2000) or schizophrenia patients treated with "typical" antipsychotics (Kumari et al. 2000) exhibited PPI deficits compared to normal controls, while PPI in schizophrenia patients medicated with atypical antipsychotics (Kumari et al. 2000) or a mixture of typical and atypical antipsychotics (Weike et al. 2000) did not differ significantly from normal controls. In clinician-driven practice, the pathway by which a given patient (or group of patients) is treated by atypical antipsychotics is determined by many disparate factors (i.e. specific symptoms, insurance company or institutional policies, drug prices, etc.). Thus, there may be many uncontrolled factors that determine why a given patient is treated with a typical versus an atypical antipsychotic medication. A between-subject experimental design does not control for the likely neurobiological differences between groups of patients who are treated with typical antipsychotics (who may possible be more likely to respond clinically to, and be tolerant of, side effects

Table 3 Effect of antipsychotic medications in schizophrenia patients. All stimuli are white noise unless frequency in Hz is specified

Type of medication	Effect on PPI	Reference	Eye	Background	Startle stimuli	Prepulse stimuli	ISI (ms)
Typical antipsychotics	PPI deficits found	Kumari et al. (2000)	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Atypical antipsychotics	Normal PPI (cross-sectional study)	Kumari et al. (2000)	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Typical antipsychotics	PPI deficits found	Perry et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Atypical antipsychotics	PPI deficits found	Perry et al. (2001)	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120
Typical antipsychotics	Normal PPI (cross-sectional study)	Weike et al. (2000)	L	Unspecified	50 ms 105 dB	20 ms 85 dB 1000 Hz	30, 60, 120, 240
Atypical antipsychotics	Normal PPI (cross-sectional study)	Weike et al. (2000)	L	Unspecified	50 ms 105 dB	20 ms 85 dB 1000 Hz	30, 60, 120, 240
Clozapine	Normal PPI (cross-sectional study)	Kumari et al. (1999)	R	70 dB	40 ms 115 dB	20 ms 85 dB	30, 60, 120

from high potency dopamine receptor blockade), versus groups of patients who are treated with atypical antipsychotics (and are thereby more likely to be clinically unresponsive to or less tolerant of the side effects from high potency dopamine receptor blockade). In any case, without the necessary longitudinal and controlled crossover studies, it is clearly premature to definitively conclude that atypical antipsychotics actually "normalize" PPI in schizophrenia patients.

Future directions and caveats

This paper has reviewed developments in human studies of PPI in a neutral, uninstructed paradigm. Three areas have been covered in most depth. First, we discussed parametric influences on PPI, with an emphasis on the impact that differences in these parameters might have on the outcome of PPI measures in human studies of psychopathological states and drug effects. Second, we described studies reporting deficits in PPI in several clinical populations, with an emphasis on schizophrenia spectrum disorders. We discussed the substantial variability across these studies, in terms of stimulus parameters and other aspects of experimental design that may account for discrepant results (see Table 1). Third, we reviewed the rapidly developing literature of pharmacological studies of PPI in humans, with a focus on the interplay of translational human and animal model studies (addressed in the two accompanying articles – Geyer et al. 2001; Swerdlow et al. 2001d in this issue). Within these three areas – parametric studies, clinical populations, and pharmacological studies of PPI – future investigators will face numerous important challenges and encounter a great number of opportunities.

It will be increasingly important to understand the neurobiological underpinnings of the various parametric influences on PPI. For example, which brain substrates are responsible for the sensitivity of long – but not short – ISI PPI to attentional manipulations (Dawson et al. 1993) and which paradigms can best elicit attentional effects? Armed with such information, investigators can develop innovative strategies for applying targeted experimental parameters towards addressing specific questions within a particular clinical population. More generally, it will become increasingly important for investigators to acknowledge and address the differences in experimental parameters that often preclude a simple comparison of key findings across different laboratories. Apparent inconsistencies in the literature, in so much as they reflect parametric differences across studies at first appear to be only problematic, but they might also provide important clues to the neurobiology of schizophrenia. Equally important is the fact that apparent "consistencies" in the literature must be reviewed critically, to determine whether experimental parameters were sufficiently comparable across studies allow us to view similar outcomes as being truly "consistent" on a phenomenological and neural substrate basis.

A similar acceptance of parametric consistency should be made in studies of different clinical populations. For example, when we conclude that "disorders X and Y both exhibit PPI deficits", or that one, but not the other, exhibits such deficits, we must clearly convey whether this statement reflects the outcome of studies performed with the same, or different, stimulus parameters. It seems possible, perhaps even likely, that many different clinical populations might exhibit PPI deficits under a variety of different experimental conditions, each of which has different neurobiological determinants.

Another critically important challenge for future studies will be to understand findings of PPI deficits within the context of other convergent and divergent experimental measures of inhibitory function. It is increasingly important to study PPI in combination with other neurobiological measures, such as P50 gating, anti-saccade measures, and latent inhibition, to determine the normal inter-relationships of these measures, as well as their relationship in clinical populations in which these measures are concordant versus discordant. For example, at first glance, it seems likely that individuals in whom PPI deficits reflect pathology only within the basal ganglia or pons might exhibit normal P50 gating, because this latter "gating" measure of cortical event related potentials might primarily reflect abnormalities at a cortical level. Yet, it is also possible that deeper structures and circuits mediate P50 suppression, as opposed to the generation of the P50 wave. In contrast, "concordance" among measures such as PPI and P50 gating might point to possible common sources of normal functioning and pathology, for example, within limbic or frontal cortical regions. Ultimately, patterns of concordance and discordance across a number of these measures might be used to segregate clinical populations, to test hypotheses across a number of domains, from pathophysiology to treatment.

Thus, as with many behavioral and psychophysiological measures, studies of PPI will benefit greatly from its differential convergence with other biological measures, even beyond those measures specifically related to inhibitory functions. Strategies are being developed for the use of PPI together with measures ranging from functional outcome, social cognition, neuroimaging to genetic mapping. Each of these uses may require new strategies for overcoming specific problems. For example, the optimal use of PPI in combination with fMRI will require new strategies, such as the use of tactile stimuli and block designs, to deal effectively with the complex acoustic and magnetic fMRI environment (e.g. Swerdlow et al. 2001c). Genetic studies of PPI in schizophrenia probands and family members may need to adopt strategies to overcome the potential impact of atypical antipsychotics in "normalizing" the critical phenotype – deficient PPI – for these genetic studies. This is not an isolated problem, since other disorders, such as hypertension, are studied in a context where probands are being effectively treated for the endophenotype being examined. Despite these interesting challenges, it is clear that a careful consideration of such complex issues is demanded by the greatly increased scientific power resulting from the convergence (and the divergence) of these different measures across biological domains.

Future studies in human clinical populations will benefit greatly from the systematic assessment of "known lesion" groups. These studies might include thorough parametric examinations of patients who have a known and relatively circumscribed neurobiological insult, such as patients with Huntington's disease, Parkinson's disease, well-defined strokes, or well-characterized neurosurgical injuries or manipulations. Profiles of PPI measures across a range of stimulus parameters in these patient groups could serve as a critically important anatomical "guide" for more complex or "anatomically distributed" disorders, such as schizophrenia.

In the area of pharmacological studies of PPI in humans, there is a need for strategies that will make full use of the translational power of PPI paradigms (see Geyer et al. 2001; Swerdlow et al. 2001d, this issue). A host of issues – from subject variability to ethical constraints – make human neuropharmacological studies extremely complex and labor-intensive. New approaches may be needed to insure that their information yield is maximal, and equally important, to insure that the rigors involved in experimentation do not lead us to accept conclusions based on less than conclusive findings regarding issues from full dose response curves, to the time and route of drug administration, to time of testing. Some of these new strategies might be adapted from preclinical pharmacological studies of PPI (e.g. Swerdlow et al. 2001a, 2000c). Studies will likely need to become increasingly precise and replicable in terms of methods of drug delivery, dosing, and monitoring of blood levels. Beyond experimental strategies, however, it will be important to identify drugs that can safely and effectively probe the major neurochemical substrates of PPI in humans, particularly the dopaminergic, glutamatergic, and serotonergic systems. This will be the first step in reconciling apparent differences in the regulation of PPI across species by some (e.g. NMDA and serotonin) but not other (e.g. dopamine, nicotine) neurochemical systems. The exciting potential for the use of infra-human primates as a species "bridge" in these pharmacological studies is only beginning to be explored (Linn and Javitt 2001).

Among studies of patient populations, medication effects present a challenging set of issues for PPI studies. In many cases, some useful information can be gleaned from existing, largely cross-sectional and relatively uncontrolled findings, but the use of controlled longitudinal, cross-over designs to allow within-subject comparisons may be particularly critical for understanding the impact of antipsychotic medications on PPI in schizophrenia. Also, it will be important to see how changes in PPI relate to changes in social and functional outcome. Certainly, ethical issues of medication changes, and specifically the use of typical instead of atypical antipsychotics need close and compassionate scrutiny, and may potentially limit our experimental options. If such studies confirm a "normalizing" impact of atypical antipsychotics on PPI in

schizophrenia, this finding will clearly enhance our ability to study and fully understand PPI deficits of the pathophysiology of this complex group of disorders. In this case, creative strategies for studying unmedicated clinical subjects, in prodromal or "first-break" designs, as well as family studies, will become increasingly important.

Even with the extensive array of informative human studies of PPI that are described above, and the opportunities for advances in future studies, some levels of analysis of PPI will remain best studied in complementary animal model studies. The ease and precision with which the experimenter can control the characteristics of the comparison groups (e.g. age, "drug history", genetic strain, etc.), while applying differing pharmacological, developmental, genetic, knock-out and knock-in, and lesion interventions in laboratory animals is particularly wide ranging and potentially informative. It is these cross-species strategies that are the subject of the following two papers by Geyer et al. (2001) and Swerdlow et al. (2001d) in this issue.

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