First publ. in: Psychopharmacology 156 (2001), 2/3, pp. 259-265

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# The effect of neuroleptic medication on prepulse inhibition in schizophrenia patients: current status and future issues



**Abstract** *Rationale*: Prepulse inhibition (PPI) of the startle reflex is a powerful tool for investigating sensorimotor gating in both animals and humans. Evidence of impaired PPI in patients with schizophrenia suggests that PPI performance might serve as a promising model to investigate the neurobiological mechanisms of this disorder. Animal data show that experimentally induced PPI deficits can be removed by the administration of antipsychotic agents. Recent clinical studies suggest that neuroleptic medication is capable of improving deficient PPI performance in schizophrenia patients as well. *Objectives*: The present paper reviews the published data on PPI performance in schizophrenia patients, focussing on medication effects. Using a modified meta-analytic approach, the consistency of PPI deficits in schizophrenia patients across studies is explored. In particular, methodological issues of defining PPI deficits and assessing PPI improvements are considered. *Method*: Literature search produced 12 original studies that investigated PPI performance in schizophrenia patients using comparable experimental conditions. Percentage change scores were calculated to compare the actual amount of PPI observed in schizophrenia patients and healthy controls across studies. *Results*: Results revealed that the amount of PPI in medicated schizophrenia patients was fairly consistent across all studies. For medicated schizophrenia patients, the amount of PPI varied between 30% and 65% for the critical lead intervals. Moreover, medicated patients showed around 20% less PPI than healthy controls. Whether these group differences were statistically significant depended on the composition of the control group that showed large variability across studies. *Conclusions*: To delineate the effects of neuroleptic medication on PPI performance more precisely, future research should not further rely on between-group comparisons. Rather, future clinical research should take advantage of longitudinal designs to disentangle state-dependent medication effects from more stable, trait-linked factors that contribute to PPI deficits in schizophrenia.

**Keywords** Prepulse inhibition · Schizophrenia · Neuroleptic medication · Startle reflex

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The magnitude of the startle response – a fast protective reflex to an unexpected intense stimulus with rapid onset – is reduced if a weak sensory event (prepulse) is presented at brief intervals (i.e., between 30 ms and 500 ms) prior to the startle eliciting stimuli. This phenomenon is called prepulse inhibition (PPI) and has been observed across a wide range of stimulus intensities and modalities in animals (Ison and Hammond 1971; Hoffman and Ison 1980, 1992) and humans (see reviews by Graham 1975; Anthony 1985; Filion et al. 1998; Blumenthal 1999). While the "whole-body" startle response – measured as cage floor displacement – is most often used in animals, the startle eyeblink is recorded as the fastest and most reliable component of the reflex sequence in humans. Although many different procedures have been used to quantify the startle eyeblink response, most investigators now record the electrical activity over the orbital portion of the orbicularis oculi muscle (Berg and Balaban 1999). The most commonly used startle eliciting stimulus in human research is a 50-ms burst of white noise, usually combined with acoustic tone or noise prepulse stimuli at varying intensities. For 60-ms and 120-ms lead intervals (i.e., the prepulse precedes the probe by 60 ms or 120 ms), PPI has turned out to be a very robust phenomenon that occurs in over 90% of normal human volunteers who exhibit a normal startle eyeblink response (Graham 1979).

PPI is viewed as reflecting the action of an automatic and involuntary sensorimotor gating mechanism that operates to selectively protect the initial processing of a weak stimulus (Graham 1975, 1992). Accordingly, PPI can be obtained during sleep (Silverstein et al. 1980) or

while subjects are engaged in a secondary sensory intake task (e.g., reading a book or watching TV; Blumenthal 1999). Moreover, PPI is obtained at the very first presentation of the lead stimulus and, thus, does not depend on learning. Finally, PPI can be observed in virtually all mammals and is, therefore, particularly amenable to animal modeling. Probably the most interest in PPI grew from the observation that schizophrenia patients show impairments in the inhibition of the startle response by weak prepulses.

Braff and coworkers were the first to report that schizophrenia patients have a deficit in this sensorimotor gating mechanism (Braff et al. 1978). In this study, a mild tone (71 dB) served as the prepulse and a burst of white noise (104 dB) as the startle stimulus. [1]Inpatients with schizophrenia showed impaired PPI relative to normal controls which was most pronounced at the 60-ms and 120-ms lead intervals, although the between-group comparison was only significant for the 60-ms lead interval. These findings were replicated and extended by two additional studies, showing that reduced PPI in schizophrenia inpatients can also be obtained with a tactile startle eliciting stimulus (Braff et al. 1992) and with different prepulse intensities, ranging from 75 dB to 90 dB (Grillon et al. 1992). These initial findings suggested that impaired PPI might indicate a stable sensorimotor gating dysfunction in schizophrenia at the level of automatic stimulus analysis and might, therefore, serve as a valuable tool to study the neurobiology of this disorder.

Stimulated by these findings, the PPI paradigm has been used extensively in animal research over the past 15 years to delineate the neurobiological underpinnings of this phenomenon, leading to a sophisticated model of the neurobiology of deficient PPI in the rat (see recent reviews by Koch and Schnitzler 1997; Swerdlow and Geyer 1998; Koch 1999; Swerdlow et al. 2000). In the rat, impaired PPI can be experimentally induced by a variety of pharmacological manipulations affecting neurotransmitter systems that are hypothesized to be dysregulated in schizophrenia. The systemic administration of direct or indirect dopamine agonists (apomorphine and D-amphetamine), serotonin agonists, or non-competitive *N*-methyl-D-aspartate (NMDA) antagonists (dizocilpine), as well as specific lesions that lead to dysfunctional glutamate–dopamine interactions result in substantial PPI deficits in rodents (for an extensive review see Swerdlow and Geyer 1998). Importantly, these experimentally induced PPI deficits can be removed by the administration of antipsychotics in the rat. According to these animal data, neuroleptic medication should also have an effect on PPI deficits in humans.

Starting from this hypothesis, Weike et al. (2000) compared PPI performance in five unmedicated, acutely decompensated and 20 medicated schizophrenia patients. While the unmedicated patients showed a complete disruption of PPI that was obvious for the 60-ms and 120-ms lead intervals, i.e., for both critical PPI conditions, medicated schizophrenia patients exhibited a substantial PPI of around 50% for 60-ms and 120-ms lead intervals. These data suggest that – analogous to animal data – PPI deficits can be removed by neuroleptic medication in schizophrenia patients. It has to be noted, though, that the amount of PPI in medicated schizophrenia patients was still smaller than that obtained for the healthy control group. These differences, however, were statistically not significant in the between-group comparison. Moreover, the results of this study revealed a substantial co-variation between the amount of PPI and the severity of positive symptoms within the group of schizophrenia patients, while no such relationship was found for the negative syndrome or general psychopathology. That is, those patients displaying a positive syndrome despite being medicated also showed impaired PPI performance. These data suggested that removal of PPI deficits in schizophrenia patients might be related to the clinical potential of neuroleptic medication.

Animal data indicate that different neuroleptic medication might operate on different systems mediating PPI deficits in the rat and, therefore, might be differentially effective in restoring PPI performance. While typical neuroleptic medication (e.g., haloperidol) is capable of removing PPI deficits induced by dopamine agonists (Mansbach et al. 1988; Swerdlow et al. 1994), it is ineffective to remove phencylidine-induced PPI deficits (Keith et al. 1991). By contrast, atypical medication (e.g., clozapine), characterized by a broader pharmacological profile, can remove apomorphine- and PCP-induced PPI deficits in rodents (Swerdlow et al. 1991; Bakshi et al. 1994).

Given these findings, Kumari and coworkers investigated whether atypical medication is more effective in removing PPI deficits in schizophrenia patients than typical neuroleptics. In two recent studies, PPI performance was assessed in schizophrenia patients receiving either typical or atypical neuroleptics (Kumari et al. 1999, 2000). Both studies revealed that schizophrenia patients receiving atypical medication exhibited the same amount of PPI as healthy controls. Only those patients receiving typical medication showed significantly less PPI than healthy controls. These group differences, however, were limited to short lead intervals (30 ms and 60 ms). Similar to the results of Weike et al. (2000) both groups of typically and atypically treated schizophrenia patients exhibited PPI of about 50% for the 120-ms lead interval. Taken together, these studies suggest that neuroleptic medication is capable of substantially improving deficient PPI performance in schizophrenia patients. In particular, atypical medication seems to alleviate PPI deficits in schizophrenia patients. It is important to note that Kumari et al. (1999, 2000) also used a between-group

[1] In PPI studies with college student samples, intensities of auditory startle probe stimuli most often vary between 95 dB and 100 dB [see Berg and Balaban (1999) for methodological issues on startle elicitation]. In clinical research with schizophrenia patients, however, startle probe intensity is higher and varies between 104 dB and 118 dB, to reduce the number of non-responders in the clinical samples

**Table 1** Amount of prepulse inhibition (PPI) in medicated, stable schizophrenia patients and healthy controls in 12 original studies examining PPI performance in schizophrenia patients in a passive attention paradigm

| | Medicated stable schizophrenia patients | | | Control subjects | | |
|---|---|---|---|---|---|---|
| | Amount of PPI (Δ%) at lead interval (ms) | | | Amount of PPI (Δ%) at lead interval (ms) | | |
| | 30 | 60 | 120 | 30 | 60 | 120 |
| 1. Braff et al. (1978) | 30 | 40 | 45 | 50 | 80 | 85 |
| 2. Braff et al. (1992) | 15 | 30 | 45 | 35 | 55 | 70 |
| 3. Grillon et al. (1992) | | | 30 | | | 75 |
| 4. Perry and Braff (1994) | | | 55 | | | |
| 5. Karper et al. (1996) | | | 50 | | | |
| 6. Braff et al. (1999) | | 45 | | | 65 | |
| 7. Perry et al. (1999) | | | 65 | | | |
| 8. Kumari et al. (1999) | 15 | 30 | 55 | 25 | 50 | 60 |
| 9. Weike et al. (2000) | 20 | 50 | 50 | 30 | 60 | 60 |
| 10. Kumari et al. (2000) | 20 | 30 | 50 | 25 | 45 | 60 |
| 11. Parwani et al. (2000) | 45 | 45 | 55 | 65 | 65 | 90 |
| 12. Cadenhead et al. (2000) | 30 | | 65 | 45 | | 60 |
| Weighted mean | 25 | 40 | 50 | 40 | 60 | 70 |

Note: all these studies used acoustic prepulses and acoustic probe stimuli. Prepulse intensities varied between 71 dB and 86 dB and probe intensities varied between 104 dB and 118 dB. Two studies (no. 3 and no. 6) varied prepulse intensities instead of lead conditions. For these two studies, the 85-dB and 86-dB prepulse intensity conditions were selected for the analysis. Some studies (nos. 1, 2, 3, 10, and 12) did not report the exact percentage change scores. Therefore, the amount of PPI was estimated using the figures reported in the publication. In these instances, the amount of PPI could not be determined with very high precision. To provide a reasonable estimation of the amount of inhibition, the estimated and reported change scores were rounded up or down in 5% steps. The amount of PPI was calculated as: PPI (Δ%)=100×(magnitude in the control condition-magnitude in each lead condition)/magnitude in the control condition. The weighted means were calculated by weighting the amount of PPI in each study by the actual sample size

comparison to assess the neuroleptic drug effects. As will be elaborated in more detail below, the between-group comparison of PPI performance in schizophrenia patients and controls, however, might not be recommended to test the differential efficacy of different neuroleptic medications, since some unique subject characteristics might be confounded with the medication effects. In support of this issue, one study revealed that the patient's age at schizophrenia onset was related to their PPI performance (Kumari et al. 2000). In this study, early onset of schizophrenia co-varied with less pronounced PPI. Thus, the findings of neuroleptic medication effects on PPI performance in schizophrenia patients have to await replication in a longitudinal design (see below).

How can these suggestive new findings be related to the results of the initial studies (Braff et al. 1978, 1992; Grillon et al. 1992) observing marked and significant PPI deficits in schizophrenia patients relative to healthy controls. In these studies, the schizophrenia patients were also mostly medicated (49 of 53), and those four patients who did not receive neuroleptic medication were described as clinically stable. It can be assumed – admittedly speculatively – that most patients in the early studies received typical neuroleptic medication. As discussed above, atypical medication might be superior in the amelioration of PPI deficits. Overall consistent with this hypothesis, Cadenhead et al. (2000) also found less pronounced PPI deficits at the 120-ms lead interval in a sample of schizophrenia patients of whom approximately 55% received atypical medication. Thus, the composition of the schizophrenia group with respect to type of medication might explain the finding of more pronounced PPI deficits in the early studies than in the more recent ones.

Taken together, there is accumulating evidence that neuroleptic medication can remove PPI deficits to a certain extent in schizophrenia patients and that atypical medication might be more effective in doing this, at least for shorter lead intervals. While these findings provide interesting perspectives, there are still some caveats that need to be considered. There is no statistical evidence that atypical medication removes PPI deficits in schizophrenia patients more effectively than typical medication. In neither of the studies mentioned above were the between-group comparisons of typically and atypically treated patients statistically significant (Kumari et al. 1999, 2000; Cadenhead et al. 2000; Weike et al. 2000[2]). Thus, the observed differential effects of typical and atypical medication appear to be modest. Moreover, PPI deficits in typically treated schizophrenia patients
relative to controls only occur for short lead intervals (30 ms and 60 ms). At lead intervals of 120 ms, typically treated schizophrenia patients did not differ from healthy controls in all four recent studies mentioned above. With regard to the earlier findings of clearly impaired PPI in medicated schizophrenia patients, it is

[2] Weike et al. (2000) tested a sample of 20 medicated schizophrenia patients. In this sample, 11 patients received typical and 9 patients atypical neuroleptic medication. No significant differences in PPI performance were detected in a comparison between both groups

obvious that the distinction between typical and atypical medication is not sufficient to account for the differential PPI performance in schizophrenia patients across various studies.

To elaborate the factors that may contribute to PPI performance in schizophrenia patients more precisely, we took a new look at the empirical database of PPI deficits in schizophrenia patients. Our rationale was to examine thoroughly the statistical assessment of PPI deficits to identify those sources of variance that might contribute to the different findings across studies. By definition, PPI deficits are evaluated in a two-step analysis. First, PPI is assessed by a within-group comparison, i.e., blink magnitudes to probes preceded by prepulses are compared with those that are elicited by probes presented without any prestimulation. Second, a between-group analysis examines whether the amount of PPI varies between schizophrenia patients and healthy control subjects. In order to increase the comparability between experiments, only those studies were included in our evaluation that investigated PPI performance in schizophrenia patients in a so-called passive attention condition, i.e., in which prepulses are presented without further instructions.[3] Furthermore, only those studies were included that used acoustic prepulses and acoustic probe stimuli. According to an extensive literature search, we identified 12 studies that met our criteria for inclusion.[4] Table 1 depicts the amount of PPI, expressed as percentage change scores from baseline startle amplitudes (i.e., pulse alone trials) for medicated and/or stable schizophrenia patients and healthy control subjects in these 12 studies. In some studies, no explicit percentage change scores were given; thus, these values were estimated from the figures provided in the publications. Inspection of Table 1 reveals that the data are remarkably consistent across different studies and laboratories.

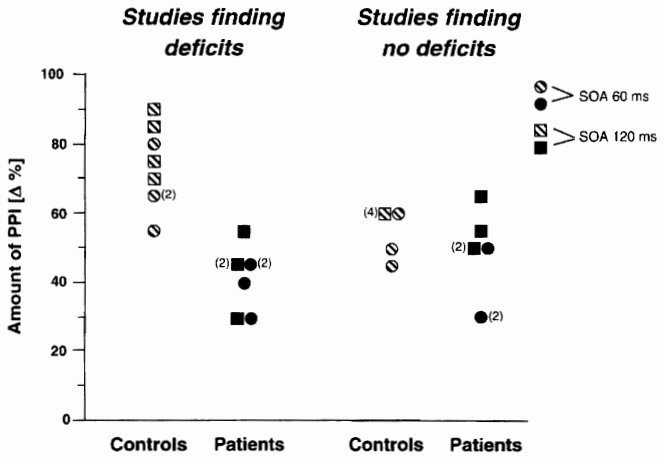


**Fig. 1** Amount of prepulse inhibition (PPI) in medicated stable schizophrenia patients and healthy controls in five different studies that found significantly less PPI in the patients' groups and in four studies that did not reveal different levels of PPI between schizophrenia patients and healthy controls

Considering the first step of PPI assessment, the data clearly reveal that both medicated schizophrenia patients and healthy controls consistently show the typical pattern of increased PPI with increasing lead intervals from 30 to 60 to 120 ms in the within-group comparisons. Moreover, all studies revealed substantial PPI in medicated schizophrenia patients, i.e., for both critical lead conditions (60 ms and 120 ms), the amount of PPI varied between 30% and 65%. Considering the second step, medicated schizophrenia patients overall showed around 20% less PPI than healthy control subjects. Whether these group differences were statistically significant in the between-group comparison, however, varied across studies. This points to an important methodological issue in the study of PPI deficits in certain clinical populations and suggests limitations of the typical assessment of PPI deficits in clinical studies. Obviously, the between-group analysis examines whether the amount of PPI varies between schizophrenia patients and healthy control subjects. This means that not only the amount of PPI in the schizophrenia patients but also that obtained in the control group determines whether PPI is relatively "deficient" in the schizophrenia patients. Figure 1 displays the amount of PPI for 60-ms and 120-ms lead intervals for schizophrenia patients and healthy controls for those studies that found significant PPI deficits in schizophrenia patients (left panel) and those that did not (right panel).

As illustrated in Fig. 1, the amount of PPI in schizophrenia patients was comparable across all studies. What differentiated those studies finding significant group differences from those that did not was the amount of PPI obtained in the healthy controls. Those studies (including our own) that did not find significant differences between patients and controls obtained less PPI in the controls (Fig. 1). One might speculate that this less

[3] There are several studies (especially from Dawson and collaborators) that have investigated the amount of PPI in schizophrenia patients using a different paradigm. In these studies, two different prepulses were presented and the patients, and control subjects were instructed to attend to one of these prepulses while ignoring the other. Although Dawson and collaborators did not find any differences between schizophrenia patients and controls under the "ignore" condition (Dawson et al. 1993, 2000; Hazlett et al. 1998), this condition was not completely comparable with the passive attention condition under which the prepulse is processed without any instruction to ignore it. Because discussion of these procedural differences would be beyond the scope of the current manuscript, the present review will be restricted to those studies that investigated startle inhibition by prepulses that were presented without any explicit instructions to either attend to or ignore these prepulses. Moreover, only these studies are directly comparable with the animal data

[4] Actually, one further original paper on PPI performance in schizophrenia patients (Bolino et al. 1994) was not included in the present overview because blink reflexes were elicited electrically. However, the findings of this study also fit nicely into the present aggregated results. Moreover, McDowd et al. (1993) presented some interesting new data on PPI in schizophrenia patients in their valuable review on sensory gating and inhibitory function in late-life schizophrenia. Although this paper is a comprehensive review, the reported original data could not be included because no information about startle response magnitudes under the control condition was provided. Therefore, we were not able to convert the illustrated raw difference scores into percentage change scores that were needed to evaluate the actual amount of PPI

pronounced PPI was due to selection criteria for control subjects, since there are many sources of variance that may contribute to the amount of PPI in controls. For example, it has been repeatedly shown that men exhibit stronger PPI than women (Swerdlow et al. 1993, 1995, 1997; Weike et al. 2000). This gender effect might be attributable to hormonal status since there is evidence that PPI varies across the menstrual cycle in women (Swerdlow et al. 1997). Moreover, personality factors seem to exert an influence on the amount of PPI (Simons and Giardina 1992; Swerdlow et al. 1995). To circumvent some of these difficulties, Kumari and coworkers (1999, 2000) investigated only carefully screened male volunteers as control subjects. Nevertheless, the PPI obtained in the control group was not as strong as in the other studies and, therefore, no significant overall group differences in the amount of PPI were observed between medicated (male) schizophrenia patients and the normal controls.

Another important issue in the evaluation of group differences in PPI performance between patients and controls concerns the critical and most sensitive lead interval to detect these differences. Since PPI is a critically time-locked phenomenon, most studies include different lead intervals in order to evaluate the typical pattern of increased PPI with increasing lead intervals from 30 ms to 120 ms. While the 60-ms and 120-ms lead intervals have proven to be optimal to detect the inhibitory effects produced by the lead stimulus, these conditions might not be the optimal ones to detect differences between patients and controls. As discussed above, several recent studies found significant group differences in PPI performance between schizophrenia patients and controls at shorter lead intervals (30 ms or 60 ms) but not at the 120-ms lead condition (Kumari et al. 1999, 2000; Cadenhead et al. 2000). It might be worth pointing out that the amount of PPI is augmented at the 120-ms lead interval if participants are instructed to selectively attend to the prepulse. No such modulation of PPI by selective attention is found for the 60-ms lead condition (for review see Filion et al. 1998). Therefore, it might be important in future studies to focus more on those lead intervals (i.e., 60 ms) that are known to reliably induce PPI but are less susceptible to active selective attention effects that might increase variability of PPI performance both in patients and controls.

Taken together, the evaluation of the empirical database on PPI performance in schizophrenia reveals, on the one hand, remarkably consistent findings for the different groups of schizophrenia patients and identifies, on the other hand, an unexpected source of unwanted variability among the control subjects. More specific, PPI is not completely disrupted in medicated, stable schizophrenia patients. All studies revealed that medicated schizophrenia patients showed substantial PPI for the 60-ms and 120-ms lead intervals. Second, although there also was an overlap in PPI performance between schizophrenia patients and healthy controls, patients overall exhibited about 20% less PPI than controls. Importantly, the variability of the amount of PPI in the control group determined whether these group differences became statistically significant in the different studies. Therefore, future research on PPI performance in schizophrenia should probably focus on the delineation of those factors that influence PPI performance within each subject population. That is, on the one hand, the "normal" variations of PPI levels need to be explored more precisely within healthy subjects, while, on the other hand, specific co-variations between PPI performance and clinically relevant variables may be studied more thoroughly within schizophrenia patients. In the latter case, exploration of the relationships among PPI performance, neuroleptic medication, symptoms, and other clinical characteristics in a longitudinal, within-group design would possibly help to disentangle the state and trait factors that might contribute to relative PPI impairments in schizophrenia patients.

Regarding the trait factors that might contribute to the relative PPI impairments, animal studies revealed that genetic factors influence the amount of PPI in rodents (for review see Swerdlow and Geyer 1998; Swerdlow et al. 2000). In this context, it is important to note that there is already evidence for a stable, presumably genetically linked component of PPI deficits in humans. As repeatedly demonstrated by Cadenhead and coworkers, patients with schizotypal personality disorder showed PPI impairments comparable to those reported for schizophrenia patients (Cadenhead et al. 1993, 2000). Moreover, it was demonstrated that clinically unaffected relatives of schizophrenia patients also displayed impaired PPI relative to controls without family history of schizophrenia (Cadenhead et al. 2000). Nevertheless, although showing significantly less PPI than controls (at least, consistently in the 30-ms lead interval), all these patients and their relatives exhibited an amount of PPI that still varied around 50% for the 120-ms lead interval.

Another trait factor that might contribute to PPI impairments in schizophrenia patients has been revealed in a recent study by Kumari and coworkers (2000). In this study, patients' ages at schizophrenia onset were related to their PPI performances. Early onset of schizophrenia co-varied with less pronounced PPI. Although there have previously been negative results on this issue (Karper et al. 1996; Braff et al. 1999), it has to be mentioned that these studies were not designed to investigate this issue. Thus, these earlier studies might have too few cases of "early onset" in their patient cohort to detect such a relationship.

With regard to the state factors that contribute to PPI performance in schizophrenia, the effect of neuroleptic medication is a major issue. As discussed above, animal research has demonstrated that experimentally induced PPI deficits can be removed by systemic administration of antipsychotics. To date, there are, however, only few studies that have directly assessed the effects of neuroleptic medication on PPI in schizophrenia patients. As stated above, Weike et al. (2000) found substantial differences between unmedicated, acutely decompensated and medicated schizophrenia patients. Furthermore, in

this study, some patients – despite being medicated – still exhibited substantial PPI deficits. These patients also displayed positive symptoms comparable to those exhibited by the unmedicated, acutely decompensated patients, suggesting that PPI deficits might also co-vary with the patients' clinical symptoms. This, however, is not a reliable finding, because several studies failed to find strong correlations between PPI performance and clinical symptoms (Perry and Braff 1994; Karper et al. 1996; Kumari et al. 1999, 2000; Perry et al. 1999; Parwani et al. 2000). However, most of these studies investigated relatively stable, medicated schizophrenia patients and the correlation between psychopathology and PPI performance might depend on sufficient variability in clinical symptoms. Moreover, future studies should look more specifically at the co-variations between PPI and specific, functionally relevant symptoms instead of aggregated syndrome scales. At least two studies reported encouraging correlations between PPI in schizophrenia patients and several measures of thought disorder (Perry and Braff 1994; Perry et al. 1999).

To sum up, future research is requested to disentangle the complex relationships between state and trait factors that contribute to the observed PPI deficits in schizophrenia patients. Given the illustrated methodological limitations of single between-group comparisons, future clinical research should take advantage of longitudinal designs. Using such designs, the time course of medication effects and their differential efficacy on the amelioration of clinical symptoms as well as on PPI performance in schizophrenia can be determined. Since it is not tenable for ethical reasons to use an A-B-A design in which patients are studied repeatedly "on" and "off" medication, the measurement of PPI in schizophrenia patients should accompany their neuroleptic treatment. Moreover, the amount of PPI deficits should also be determined, if possible, before the patients receive any neuroleptic medication. During the course of treatment, it is recommended to repeatedly assess PPI performance. Longitudinal designs would also answer questions whether improvement of PPI performance precedes the amelioration of clinical symptoms or vice versa, i.e., whether PPI performance can be used to assess the clinical potential of a specific medication. Finally, these repeated-measures designs can investigate whether the state-induced changes in PPI performance can be disentangled from more stable PPI impairments that might be linked to possible, specific risk factors of schizophrenia.

**Acknowledgements** This research was supported by a grant from the Deutsche Forschungsgemeinschaft (German Research Society) to Alfons Hamm (Ha 1593/10–2).

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