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ORIGINAL PAPER

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Prepulse inhibition of the acoustically evoked startle reflex in patients with an acute schizophrenic psychosis – A longitudinal study

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Abstract Deficits in sensorimotor gating as assessed by prepulse inhibition (PPI) of the startle reflex have been reported in schizophrenia. However, the state or trait nature of these deficits and the relationships with clinical features and psychopathological symptoms are not clear. To explore these issues, we performed a longitudinal study with schizophrenia inpatients.

We examined 36 medicated schizophrenia inpatients twice in the course of an acute psychotic episode: recently after admission and after psychopathological improvement 2–3 weeks later. In addition, we examined 18 healthy control subjects twice (two weeks apart).

Relative to control subjects, patients with schizophrenia had lower PPI only in the acute, but not in the improved clinical state. Larger PPI deficits were associated with more severe formal thought disorder and bizarre behavior.

In the present longitudinal study, PPI deficits in schizophrenic patients appeared to be state dependent. Taking into account recent evidence from the literature we propose that reduced PPI may be a mediating vulnerability marker of schizophrenia: Impairments in sensorimotor mechanisms which subserve PPI of the startle reflex may both predispose individuals to develop psychosis, and, in addition, may covary with the presence of acute positive symptoms.

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Introduction

Prepulse inhibition (PPI) of the startle blink reflex is an operational measure of sensorimotor gating that serves to automatically filter out irrelevant or interfering stimuli. Prepulse inhibition was found to be reduced in numerous studies with schizophrenia patients [e. g. 5, 9, 28–30, 35, 40]. These findings reflect increased vulnerability to stimulus inundation in schizophrenia, which, in turn, may lead to cognitive fragmentation and thought disorder [10, 19, 31]. In line with this theoretical concept, impaired sensorimotor gating was found to be associated with thought disturbance in patients with schizophrenia [38, 39].

PPI deficits were demonstrated in drug-naïve schizophrenia patients [29, 30], acutely decompensated inpatients and stable outpatients with schizophrenia [37], asymptomatic first-degree relatives of schizophrenic patients [14], patients with schizotypal personality disorder [11, 14], and presumably psychosis-prone individuals [46, 47]. Based on these studies, the reduction in PPI has been often regarded as a fundamental trait or vulnerability marker of schizophrenia spectrum disorders related to genetic and/or neurodevelopmental factors that predispose individuals to manifestation of the disorder. On the other hand, PPI deficits in schizophrenic patients were found to be related to current positive symptoms [8, 48] and distractibility [22]. These findings suggest a potential influence of the current psychopathological state on PPI. In addition, neuroleptic medication has been hypothesized to reduce PPI impairments in patients with schizophrenia [20, 24, 25, 28, 48]. However, some recent studies did not reveal any significant effect of antipsychotic medication on PPI [16, 17, 30]. Thus, the relative contributions of trait and state factors to sensorimotor gating deficits in schizophrenia remain unclear, and several authors stressed

the need for longitudinal studies to clarify this issue [6, 20, 37].

In a follow-up study, Ludewig and coworkers [28] reported stable PPI deficits in medicated chronic schizophrenic outpatients whose clinical state did not change over the course of the investigation. Whereas in this study patients did not show any significant change in clinical state across the investigations, we aimed to assess PPI of the acoustically evoked startle reflex in patients with schizophrenia during an acute psychotic state and at follow-up after clinical improvement. We examined the question, whether PPI represents a stable neurobiological marker or whether it is influenced by fluctuations of the psychopathological state.

Subjects and methods

Subjects

A total of 60 medicated inpatients with an acute psychotic episode entered the study. They were diagnosed for schizophrenia according to DSM IV criteria by the use of a semi-structured interview performed by an experienced clinician. Patients were screened carefully to rule out an additional Axis I diagnosis or any neurological or medical disorder that may influence the excitability of the startle reflex. Patients with current drug abuse were excluded by an interview and a serum toxicology screen before startle testing. 20 healthy controls were recruited from the community and hospital staff of the University Hospital of Aachen. Exclusion criteria for the healthy control group comprised any psychiatric Axis I disorder, any neurological or medical disorder and current drug abuse that may influence the excitability of the startle reflex, any psychiatric Axis I disorder in a first degree relative, and any psychoactive medication.

Written informed consent was obtained from all participants after we described the experimental procedures in detail and explained that they might withdraw from the study at any time, if they wished so, without having to explain the reasons. In particular, patients were informed that withdrawal would have no impact on their further treatment. The study was approved by the ethical committee of the RWTH Aachen.

Startle examination

Blink reflex measures were performed in a quiet room. Participants were asked to relax and to look at a blank wall approximately 2 m in front of them while sitting comfortably in a recliner chair. They were told that the experiment was concerned with the behavior of simple reflexes and that during the session they would hear noises through headphones that they should ignore. All patients had their usual coffee intake in the previous 3 hours before electromyographical examination. Participants, who were smokers, had their previous cigarette about 30–60 minutes before testing.

Electromyographic activity was recorded from the right orbicularis oculi muscle with small silver/silver chloride surface electrodes filled with gel. The electrodes were placed over the lower part of the muscle. The ground electrode was fixed 2 cm below the right mastoid. Electrode resistances were less than 8 kΩ.

Reflex measures were performed using a commercially available device (SR-LAB, San Diego Instruments, San Diego, CA). Via this computerized system, EMG activity was recorded in 250 1-ms readings from pulse onset and bandpass filtered (1–1000 Hz). The filtered activity was amplified, digitized, and rectified. A digital unit was equal to 1.7 μV. For analysis, the digital signal was smoothed by averaging 10 successive points. The minimum response criterion for a peak was set at 9 arbitrary amplitude units. The acoustic stimuli were presented binaurally through headphones (TDH-39-P, Maico, Minneapolis, MN).

After an acclimation period of 5 minutes to a 65 dB(A) broadband noise that served as a continuing background noise during the session, startle-eliciting stimuli were presented that consisted of white noise bursts with an intensity of 115 dB(A) and a duration of 20 ms. In a first block, 4 pulse-alone (PA) stimuli were applied to produce early response decrement by habituation in order to achieve a more stable magnitude for PPI assessment in the second block. The second block consisted of 30 trials presented in a pseudo-randomized order. Apart from 10 PA trials, there were 20 prepulse-pulse (PP) trials with a weak acoustic prestimulation (8 dB above background noise, 20 ms in duration) being followed by the 115 dB stimulus. The interstimulus interval (ISI) from onset of prepulse to onset of stimulus was 30 ms or 100 ms (PP30 and PP100, 10 trials each). 100 ms-intervals were used instead of 120 ms-intervals applied in other studies to minimize influence of controlled attentional mechanisms [15, 21]. In a third block, 4 PA stimuli were applied to assess habituation across the session (unpublished data). The intertrial intervals varied between 8 and 22 s. The entire session lasted about 16 min.

All trials were analyzed automatically. Peak magnitudes, peak latencies, and onset latencies were determined. In responses showing two peaks, the second peak was measured [32]. Onset of the reflex response was defined by a shift of at least six digital units from baseline occurring within 18–80 ms after stimulus onset. Peak magnitudes were measured within 120 ms following the onset of the startle stimulus. In trials that showed no detectable blink response, magnitude was scored as zero and latency data were discarded. Prepulse inhibition (PPI) was calculated as a percentage score (100 x [magnitude PA trials block 2 – magnitude PP trials block 2]/magnitude PA trials block 2). Startle reactivity was defined as the mean magnitude of PA trials in block 2.

Responses were excluded if the baseline shift exceeded 50 units. Subjects with a mean peak magnitude less than 20 digital units in the first block of 4 PA trials were regarded as non-responders and were excluded from further analyses. From the 20 controls and 60 patients who entered the study, two controls and 13 patients were excluded on this criterion. This difference was not significant by chi-square analysis ($p > 0.05$). In addition, 3 agitated patients were excluded due to frequent voluntary movements with extensive electromyographic activity within 20 ms after stimulus onset (artifacts in > 33 % of all trials or > 50 % of the trials in any condition). From the remaining 44 patients, 8 subjects were examined in the acute state, but refused a second investigation for various reasons. Thus, the final samples consisted of 36 acute psychotic patients and 18 healthy controls. Medicated inpatients underwent the startle sessions within 10 days after admission to the Department of Psychiatry of the RWTH Aachen while being in an acute psychotic state (T1) and again 2–3 weeks later (T2). All 18 healthy controls were reexamined 2–3 weeks after T1 (T2).

Statistical analysis

The test-retest reliability of startle magnitude and PPI was investigated using the Intraclass-coefficient for internal consistency [45]. Data for magnitude in PA trials, PPI, onset latencies, and peak latencies were compared between patients and controls using repeated measures analyses of variance (ANOVA). Parallel analyses using nonparametric procedures yielded similar results, but are not presented. In the group of schizophrenia patients, Pearson's correlation coefficients were employed to explore the relationships between PPI and important clinical variables (age of onset of the disorder, number of psychotic episodes, duration of illness) as a well as psychopathological symptoms (total scores of SANS, SAPS and BPRS, SAPS subscale scores for hallucinations, delusions, bizarre behavior, and formal thought disorder, SANS subscale score for attentional dysfunction, scores on single items of the SAPS subscale for positive formal thought disorder). Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS (Windows, version 9.0).

Results

Demographic and clinical characteristics

Table 1 displays demographic and clinical variables of 36 patients and 18 controls. The two groups were similar in terms of age, gender, and education (ANOVA, χ^2-test, $p > 0.05$). However, the control group included a smaller percentage of smokers (χ^2-test, $p < 0.05$).

Psychopathological symptoms were rated on the day of startle testing using the Brief Psychiatric Rating Scale (BPRS) [36], the Scale for the Assessment of Negative Symptoms (SANS) [1], and the Scale for the Assessment of Positive Symptoms (SAPS) [2]. At T1, patients had moderate to severe acute psychotic symptoms. At the follow-up examination, positive symptoms (SAPS score) showed a marked remission (ANOVA, $p < 0.001$), whereas negative symptoms did not improve significantly (Table 1). All patients were medicated according to clinical considerations: They received typical (haloperidol, benperidol, flupentixol, perazine, fluphenazine) or/and atypical neuroleptics (olanzapine, clozapine, amisulpride, quetiapine), partially in combination with sedative medications (lorazepam > 1 mg/d, diazepam > 2 mg/d, thioridazine > 100 mg/d, levomepromazine > 100 mg/d) and biperidene (2–4 mg/d). About 50 % of the patients had received neuroleptic medication before admission for various time intervals. Thus, at the first time of testing, the vast majority of patients had been treated with neuroleptics for at least 10 days. Moreover, the pharmacological regimen was often changed during the course of the episode and also combinations of typical and atypical agents were given in our patient sample.

Table 1 Demographic and clinical variables of the final control and patient samples at the different times of examination, after exclusion of subjects with low magnitudes (non-responders) or frequent electromyographical artifacts (*NL* neuroleptic medication)

	Patients		Controls
Number	36		18
Gender	14 f, 22 m		6 f,12 m
Age (years)	32.7±7.5		32.6±5.3
Education (years)	15.3±4.3		16.4±2.6
Smokers (%)	47.2		27.8
Age at the onset (years)	28.1±6.3		
Number of episodes	2.3±1.6		
First episode patients (%)	38.9		
Duration of illness (years)	5.3±4.7		
	T1	T2	
Atypical NL	8	10	
Typical NL	19	14	
Combination typical + atypical NL	9	12	
Concomitant sedative medication	15	8	
Biperidene	13	14	
BPRS	42.1±10.9	33.2±8.7	
SAPS	35.1±21.8	12.5±11.6	
SANS	35.7±25.2	33.5±21.9	

Startle reactivity

Mean magnitudes in pulse alone trials (block 2) were found to be stable in normal controls (ICC = 0.70, $p = 0.004$). Schizophrenia patients (ICC = 0.68, $p < 0.0001$) exhibited lower magnitudes at T1 and T2 (Fig. 1): Repeated measures ANOVA revealed significant effects of the between-subject factor group ($df = 1, 52$, $F = 7.0$, $p = 0.011$), but not of factor time (T1/T2), ($df = 1, 52$, $F = 0.08$, n. s.) and no time x group interaction ($df = 1, 52$, $F = 0.63$, n. s.).

Because smoking, anticholinergic agents, and sedative medication may reduce startle reactivity [14, 26, 41, 43], we applied a univariate ANOVA to examine the influence of these factors on magnitude in the patient group. Indeed, at T1 patients with a sedative co-medication (benzodiazepines or neuroleptics with low antipsychotic and high sedative potency) showed significantly smaller peak magnitudes to startle stimuli ($n = 15$, 24.7 ± 23.2 units) compared to patients who were treated with potent neuroleptics only ($n = 21$, 65.7 ± 61.9 units): ANOVA revealed a significant effect of sedative medication on startle reactivity ($df = 1, 35$, $F = 6.5$, $p = 0.02$), but no effects of anticholinergic medication ($F = 0.05$, n. s.) and smoking ($F = 0.001$, n. s.), and no significant interactions.

Prepulse inhibition

In normal controls, PPI100 (ICC = 0.77, $p < 0.0001$) was found to be more stable than PPI30 (ICC = 0.63, $p = 0.002$). Patients with schizophrenia (PPI100:

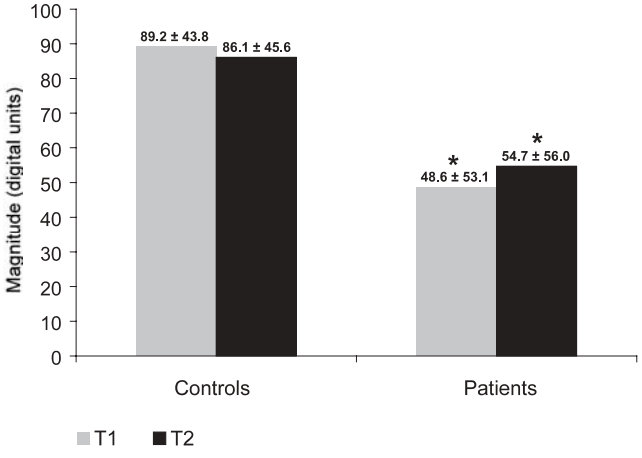

Fig. 1 Startle reactivity (mean magnitude (± SD) of pulse-alone trials in block 2) in 18 healthy control subjects and 36 schizophrenia patients in an acute psychotic state (T1) and after psychopathological improvement (T2); * statistically significant compared to controls ($p < 0.05$, ANOVA)

ICC = 0.36, p = 0.01, PPI30: ICC = 0.45, p = 0.002) showed significant PPI deficits only at T1 and only for the 100 ms trial type, but not in the trials using an ISI of 30 ms: For the 100 ms trial type (Fig. 2), repeated measures ANOVA revealed significant effects for group (df = 1, 52, F = 7.4, p = 0.009), for time (T1, T2), (df = 1, 52, F = 10.0, p = 0.003) and a significant group x time interaction (df = 1, 52, F = 19.0, p < 0.0001). All other interactions were not significant (p-values > 0.5). Using an ISI of 30 ms, PPI reduction in schizophrenia patients (Fig. 2) did not reach statistical significance: Using repeated measures ANOVA no effects for group and time emerged. Also the group x time interaction did not reach statistical significance (df = 1, 52, F = 3.1, n. s.). Group distributions for PPI are displayed in Fig. 3. When two standard deviations below the mean of the control subjects was applied as a cutoff, 5.6 % of the controls and 44.4 % of the patients had PPI 100 values below the cutoff (χ^2-test, p < 0.001).

There was no association between the PPI100 or PPI30 values and startle reactivity in schizophrenia patients (n = 36 at T1, PPI100 and reactivity: Pearson's correlation coefficient r = 0.07; PPI30 and reactivity: r = 0.18).

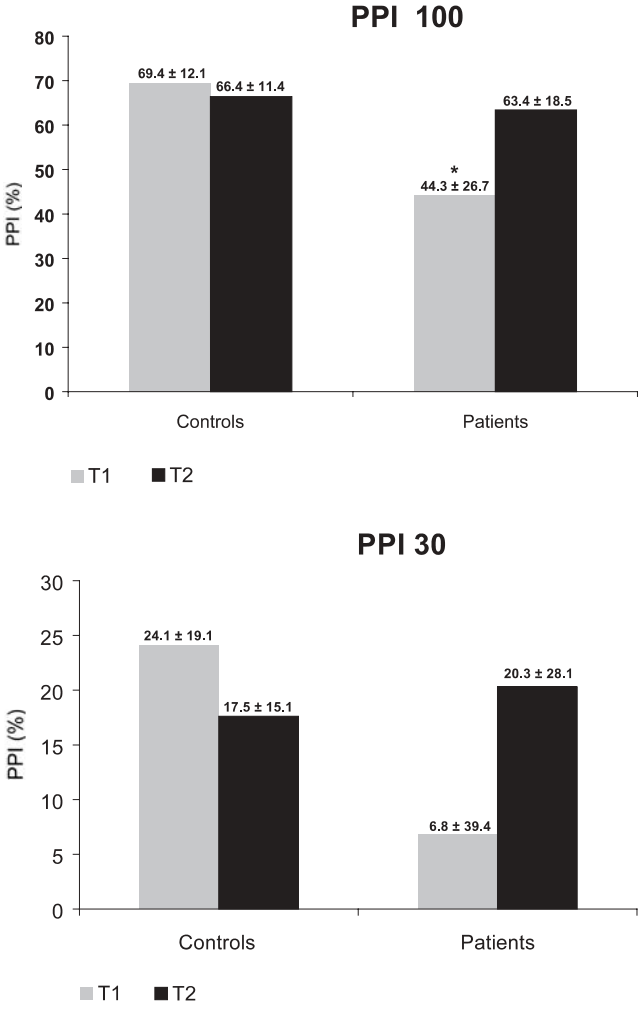

Fig. 2 Prepulse inhibition of the acoustic startle (in %) using interstimulus intervals of 100 ms and 30 ms in 18 healthy control subjects and 36 schizophrenia patients in an acute psychotic state (T1) and after psychopathological improvement (T2); * statistically significant compared to controls (p < 0.05, ANOVA)

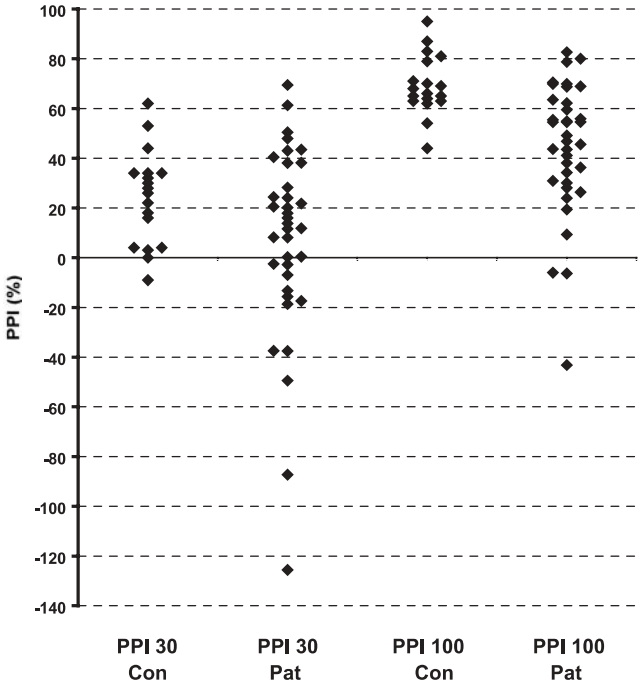

Fig. 3 Group distributions of PPI (ISI of 30 ms and 100 ms) in 36 acutely psychotic schizophrenia patients and 18 healthy controls (T1)

Peak latencies

Since it is likely that the analysis of onset latencies may be confounded by the difference of magnitudes between the patient and control group, only peak latencies were examined statistically. In controls, means of peak latencies in pulse alone trials (62.7 ± 4.5 ms) showed a significant latency facilitation in prepulse pulse trials with interstimulus intervals of 30 ms (57.5 ± 4.1 ms) and 100 ms (57.3 ± 4.8 ms) that were similar at T1 and T2. This facilitating effect was similar in the control and patient group (inferential statistics not shown).

Clinical variables, psychopathology, and sensorimotor gating

Clinical variables (age, age at onset of the schizophrenic disorder, number of psychotic episodes, duration of illness) were not reliably associated with the amount of PPI30 or PPI100 in schizophrenic patients (n = 36, T1, Pearson's correlation coefficient, all p-values > 0.10).

Nevertheless, PPI 100 deficits were significantly correlated with SAPS items of bizarre behavior (r = –0.34, p = 0.04), formal thought disorder (r = –0.47, p = 0.004), derailment (r = –0.39, p = 0.02), tangentiality (r = –0.37,

$p = 0.03$), incoherence ($r = -0.49$, $p = 0.003$), illogicality ($r = -0.53$, $p = 0.001$), circumstantiality ($r = -0.43$, $p = 0.008$), and pressure of speech ($r = -0.35$, $p = 0.04$).

In addition, using an interstimulus of 30 ms, more severe PPI deficits were associated with formal thought disorder ($r = -0.44$, $p = 0.007$), circumstantiality ($r = -0.43$, $p = 0.01$), pressure of speech ($r = -0.38$, $p = 0.02$), distractibility ($r = -0.33$, $p = 0.049$), and clanging ($r = -0.41$, $p = 0.01$).

No significant correlations were found between PPI deficits and negative symptoms (SANS total score, SANS subscales) and BPRS ratings.

Discussion

The most important finding of the present longitudinal study in medicated patients with schizophrenia is that PPI deficits of the acoustic startle were present only in the acute psychotic state and not in the follow-up examination; impairments of PPI in schizophrenic patients therefore appeared to be state dependent. In particular, patients revealed a highly significant reduction of PPI when an interstimulus interval of 100 ms was used, whereas the group difference of PPI with an interstimulus interval of 30 ms did not reach statistical significance. This difference might be due to the lower temporal stability of PPI 30 in normal subjects – a finding that is consistent with previous reports [13, 28].

In addition, we found a reduced startle reactivity with smaller magnitudes in pulse alone trials compared to normal controls, which has not been reported in the literature before. It is important to point out that PPI deficits were not due to the overall smaller reflex magnitudes. First, as generally accepted in the literature, the effects of prepulses were assessed using percentage, and not difference scores. Second, no association was found between startle reactivity and PPI in correlation analyses. Thus, startle magnitude and PPI appeared to be independent startle parameters in the present study. The reduced startle reactivity may have been due primarily to the concomitant sedative medication. It is well known that benzodiazepines lead to a massive reduction of startle magnitude [41, 43]. In support of this conclusion, the acute psychotic patients who were under mandatory sedative comedication exhibited significantly smaller magnitudes than the remaining patients who were treated only with potent neuroleptics.

In the present study, psychopathological symptoms were assessed in detail. In acutely psychotic patients, significant correlations emerged between PPI deficits and some aspects of formal thought disorder and bizarre behavior. Both Bleuler [3] and Kraepelin [23] originally emphasized that formal thought disorder might be related to impaired cognitive control and disturbed attentional processes. In the following decades – supported by a host of empirical evidence – many researchers shared the idea that deficits in automatic and controlled information processing may be core features of schizophrenia [review in: 7, 33]. These deficits of inhibitory mechanisms in the basic processing of stimuli may be crucial not only for the suppression of external, but also of internal stimuli, such as intruding thoughts and impulses [18]. Our data are in line with this hypothesized relationship between impairments of preattentive stimulus processing and schizophrenic symptoms, and they are in agreement with previous studies demonstrating associations between PPI deficits and positive symptoms [8, 48], distractibility [22], and formal thought disorder [38, 39]. Nevertheless, in our study some patients exhibited a normal amount of PPI despite clinically obvious attentional dysfunctions and severe positive formal thought disorder. It cannot be ruled out that neuroleptic treatment will have normalized preexisting PPI impairments after one week of treatment. Nevertheless, reduction of PPI does not appear to be merely a neurophysiological correlate of exacerbated psychopathological phenomena and limited attentional capacity to process stimuli during acute psychosis, since the regular latency facilitation by prepulses in our patient sample argues for a normal detection of the weak prepulse. Rather, PPI deficits appear to reflect a fundamental impairment of central gating mechanisms in preattentive stimulus processing that may possibly contribute to the development of schizophrenic symptoms by stimulus inundation [10, 19, 31].

The study is limited by the fact that the effect of neuroleptic medication could not be analyzed reliably. In statistical comparisons between patients who were treated with atypical versus typical agents we did not find any significant group differences (statistics not shown). However, the choice of treatment was biased by several uncontrolled factors and the question of the influence of different types of neuroleptic medication on PPI cannot be examined based upon the present data. The question whether atypical agents might be superior to typical antipsychotic medication remains an objective for double blinded, controlled studies.

Based on our data and studies of authors who regard PPI impairment as a fundamental trait marker [e. g. 11, 14, 29, 30, 46], we propose that reduction of PPI may represent a mediating marker of schizophrenia, i. e. an indicator that shares characteristics of both vulnerability and episode markers [34]; on such a marker, asymptomatic vulnerable individuals exhibit differences compared to less predisposed subjects, and the deviation increases with the development of acute positive symptoms triggered by different stressors. In our concept, psychosis-prone individuals, schizotypal subjects, and asymptomatic subjects predisposed for schizophrenia by genetic or neurodevelopmental factors may show PPI deficits, which are less robust than PPI deficits in patients with an acute psychotic episode. In line with previous work, PPI deficits may correlate with the severity of positive symptoms [8, 48] and improve with neuroleptic treatment and remission of positive symptoms. This concept is in line with the idea of Saccuzzo and Braff [42] that information processing dysfunction is re-

garded "as both an enduring trait of patients with schizophrenia spectrum disorders and as a state that probably covaries with the presence of thought disorder and psychotic symptoms in psychotically disordered patients". In line with the report of Weike et al. [48], it may be reasonable to argue that – similar to findings using backward masking paradigms [42] – PPI deficits may be normalized in patients with good prognosis, whereas they may persist in some patients with ineffective neuroleptic treatment.

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