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Abstract

BACKGROUND: Schizophrenia patients exhibit impairment in prepulse inhibition (PPI) of the acoustic startle response (ASR), which is commonly interpreted as a sensorimotor gating deficit. To date, it is unclear when these gating deficits arise. Results of animal studies and some human data suggest that PPI deficits are in part genetically determined, such that gating deficits could be present before the onset of a full-blown psychosis. To test this assumption, we investigated PPI of ASR in individuals with prodromal symptoms of schizophrenia and patients with first-episode schizophrenia. METHODS: Startle reactivity, habituation, and PPI of ASR, as well as a neuropsychological test battery, were assessed in 54 subjects with prodromal symptoms of schizophrenia (35 early and 19 late prodromal subjects), 31 first-episode schizophrenia patients (14 unmedicated, 17 medicated), and 28 healthy control subjects. Patients were also examined with the Positive and Negative Syndrome Scale and the Global Assessment of Functioning Scale. RESULTS: Prodromal subjects and unmedicated patients with first-episode schizophrenia showed significant PPI deficits, whereas schizophrenia patients treated with risperidone had almost normal PPI. Startle reactivity decreased with greater severity of symptoms (control subjects, early prodromal group > late prodromal group > unmedicated first-episode patients) but was almost normal in the medicated patients. With respect to habituation, prodromal subjects and schizophrenia patients did not differ from healthy control subjects. CONCLUSIONS: PPI disruption is already present in a prodromal state of schizophrenia, but startle reactivity deficits seem to emerge with the onset of acute psychosis.
Impaired sensorimotor gating of the acoustic startle response in the prodrome of schizophrenia

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Abstract

Background: Schizophrenia patients exhibit impairment in prepulse inhibition (PPI) of the acoustic startle response (ASR) which is commonly interpreted as a sensorimotor gating deficit. To date, it is unclear when these gating deficits arise. Results of animal studies and some human data suggest that PPI deficits are in part genetically determined, such that gating deficits could be present before onset of a full-blown psychosis. To test this assumption, we investigated PPI of ASR in individuals with prodromal symptoms of schizophrenia and patients with first-episode schizophrenia.

Methods: Startle reactivity, habituation, and PPI of ASR as well as a neuropsychological test battery were assessed in 54 subjects with prodromal symptoms of schizophrenia (35 early and 19 late prodromal subjects), 31 first-episode schizophrenia patients (14 unmedicated, 17 medicated), and 28 healthy controls. Patients were also examined with the Positive and Negative Symptom Scale and the Global Assessment of Functioning Scale.

Results: Prodromal subjects and unmedicated patients with first-episode schizophrenia showed significant PPI deficits, whereas schizophrenia patients treated with risperidone had almost normal PPI. Startle reactivity decreased with greater severity of symptoms (controls, early prodromal group > late prodromal group > unmedicated first-episode patients) but was almost normal in the medicated patients. With respect to habituation, prodromal subjects and schizophrenia patients did not differ from healthy controls.

Conclusions: PPI disruption is already present in a prodromal state of schizophrenia but startle reactivity deficits seem to emerge with the onset of acute psychosis.
Introduction

Since the publication of Kraepelin’s (1) and Bleuler’s (2) findings, attentional and information-processing deficits are considered to constitute core symptoms of schizophrenia and schizophrenia spectrum disorders and impairments in the processing of preattentive inhibitory stimuli – also referred to as “sensorimotor gating” – appear to play a crucial role in the pathogenesis of schizophrenia (3-7).

Prepulse inhibition (PPI) of the acoustic startle response (ASR) has been firmly established as an operational measure of sensorimotor gating (8). PPI is defined as a substantial reduction of the amplitude of the startle reflex that occurs when a distinctive non-startling stimulus is presented 30-500 ms prior to the startling stimulus (9). It was proposed that the mechanism underlying PPI regulates sensory input by filtering out irrelevant or distracting stimuli in order to prevent sensory information overflow and to allow for selective and efficient processing of relevant information (10).

Diminished PPI has been consistently demonstrated in patients with schizophrenia (8,11-15) and schizotypal personality disorder (11,16). The PPI deficit in schizophrenia is supposed to reflect a central abnormality underlying the disease; both neuroanatomical and neurochemical factors have been implicated on the basis of animal studies, which suggest contributions of diverse neurotransmitter systems, and particular functional association with multiple loci in the cortico-striato-pallido-thalamic (CSPT) circuitry (17,18).

To date, it is unclear whether these gating deficits arise with or after the onset of an acute psychosis or if these deficits already exist before onset of schizophrenia. However, the expression of PPI seems subject to strong genetic influences, as evidenced by the presence of significant differences in PPI between inbred strains of rodents (19-21). It has been recently estimated that the heritability of PPI in schizophrenia patients and their families is about 32%, whereas another study reported a heritability of 50% within a healthy twin sample (22,23). Furthermore, sibling pairs (one with and one without schizophrenia) show a relatively high correlation in PPI (r=0.66) (11). Recently, quantitative trait loci for PPI have been identified in rodents (24-26), and studies in humans suggest that mutations of the neuregulin-1, the dopamine-D3 receptor, and the serotonin-2A receptor gene affects PPI (27-29). Two studies have shown that unaffected first-degree relatives of schizophrenia patients also display PPI deficits, supporting the view that genetic influences also mediate PPI deficits in
schizophrenia (11,30). In sum, these genetic findings suggest that PPI deficits could occur already before onset of schizophrenia and, thus, PPI deficits may serve as simple indicator for the vulnerability for schizophrenia.

To test this hypothesis, we investigated PPI, startle reactivity, and habituation of ASR in subjects in a prodromal state likely to proceed to schizophrenia. The study was conducted within the frame of the German Research Network on Schizophrenia (GRNS)(31). Given that early and late stages of developing psychosis could be distinguished (31-33), we examined prodromal subjects supposed to be either in an early or a late prodromal state of schizophrenia. Whereas the early prodromal stage presents self-experienced cognitive and perceptual alterations (basic symptoms) shown as predictive for later psychosis (34), the late prodromal stage is additionally characterized by attenuated or transient psychotic symptoms (31). Moreover, we studied unmedicated and medicated first-episode patients, since antipsychotic treatment, especially with atypical agents, can improve PPI (12,15,35-39). Thus, we measured PPI in five groups: early prodromal subjects (EP), late prodromal subjects (LP), unmedicated first-episode schizophrenia patients (US), medicated first-episode schizophrenia patients (MS), and healthy control subjects (HC). We assumed that the same etiological risk factors would underlie prodromal states and schizophrenia and we therefore hypothesized that PPI disruption would already be present in groups of prodromal subjects. Based on previous findings we also expected that PPI impairments would be less marked in MS than in US.
Methods and materials

Participants

Subjects with symptoms suggestive of either early or late prodromal stages were recruited as described previously (31). In brief, subjects were screened by general practitioners, counseling services or secondary health care providers using the 17-item Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos) checklist (31). Persons scoring six points or higher were referred to the Early Recognition and Intervention Center at the Department of Psychiatry, University of Bonn, for detailed assessment with the 110-item ERIraos symptom list (31).

The criteria for the early prodromal state were based 1) either on presence of basic symptoms which were shown as highly predictive for psychosis (34) or 2) on the presence of a first-degree relative with a psychotic disorder in conjunction with a reduction of the global assessment of function (GAF). In contrast, subjects with attenuated positive symptoms (APS) or brief limited intermittent psychotic symptoms (BLIPS) were considered to be in a late prodromal stage, which is in line with conventional criteria used in other clinical high-risk studies (40).

Prodromal subjects and schizophrenia patients were not included if they had a diagnosis of a developmental disorder, an organic psychiatric disorder or a history of a neurological disorder, dementia or alcohol and drug abuse within the last three months prior to the study. Based on these criteria, we included 39 subjects in an early prodromal stage (EP) and 23 subjects at a late prodromal stage (LP). Two EP and two LP received treatment with atypical antipsychotics. One EP and six LP were treated with antidepressants.

The group of schizophrenia inpatients included 18 unmedicated patients (US) and 17 medicated patients (MS), both with a first exacerbation of schizophrenia according to DSM-IV criteria. The medicated schizophrenia patients had been randomly and double-blind assigned to either haloperidol (mean dose±SD: 4.6±1.6 mg, range: 3-8 mg) or risperidone (4.5±2.4 mg, range: 2-10 mg) maintenance treatment, as part of a separate clinical trial, results of which are published elsewhere (41). US were never systematically treated with antipsychotics before and none of them took an antidepressant for at
least four weeks. Two MS were also treated with antidepressants. Benzodiazepine treatment was discontinued 24 hours before ASR assessment.

Finally, 32 healthy control subjects were matched with respect to age, sex and education to the prodromal subjects. These volunteers were recruited by advertising in local newspapers, word of mouth or they were actively contacted by the investigators based on their listing as community residents. None had past or present psychiatric, neurological, or somatic disorder, and negate use of psychotropic medication or illicit drug use. Moreover, none of the control subjects reported a family history of psychiatric disorders.

This study was approved by the Ethics Committee of the Medical Faculty of the University of Bonn. After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion.

**Clinical assessment**

To ensure eligibility for the study every participant was evaluated by a *Structured Clinical Interview* (SCID-I) according to DSM-IV. Clinical symptoms were measured with the *Positive and Negative Symptom Scale* (PANSS)(42). Psychosocial functioning was assessed using the *Global Assessment of Functioning* (GAF)(43). For the estimation of verbal IQ, the *Mehrfachwahl-Wortschatz-Intelligenztest* (MWT-B) was used (44).

**Startle response measurement**

After the clinical examination, a neuropsychological test battery was administered first (these results will be published elsewhere), followed by the ASR assessment. Before each ASR assessment, all participants underwent a brief hearing test. The PPI paradigm was based on the study of Braff et al. (8) and has been described in detail in our previous work (15,45). In brief, subjects received 73 sound pulses with a power of 116 dB along with 70 dB background white noise. In 36 of the trials, the pulse was preceded by an 86-dB prepulse with an interstimulus interval (ISI) of 120 ms. The eye-blink component of the ASR was measured using an electromyographic startle system (San Diego Instruments, San Diego, CA). To ensure that PPI was not influenced by smoking withdrawal, smoking *ad libitum* was permitted before testing (46). Error trials were defined as trials in which no startle response was recorded because of a baseline shift normally due to spontaneous or voluntary blinks.
Four healthy subjects (12.5%), eight prodromal subjects (12.9%) and four schizophrenia patients (11.4%) with error trials greater than 50% were excluded from data analysis.

**Statistical analysis**

The mean percent PPI of startle amplitude was calculated using the formula:

\[ \%\text{PPI} = 100 \times \frac{\text{magnitude on pulse alone (PA) trials} - \text{magnitude on prepulse (PP) trials}}{\text{magnitude on PA trials}} \]

PA trials were divided into six blocks, each comprising six trials. Startle reactivity was assessed by calculating the mean amplitude of the first block of PA trials. To assess habituation, the linear gradient coefficient \( b \) was calculated across the six blocks of PA by the following formula:

\[ b = \frac{n \sum xy - (\sum x)(\sum y)}{n \sum x^2 - (\sum x)^2} \]

where \( x \) = block number, \( y \) = startle amplitude of PA trials per block (47). All data were analyzed using SPSS 12.0 for Windows. Because all dependent variables were normally distributed, the demographic, clinical and startle data were analyzed by analysis of variance. Given that gender, smoking, and age could have an impact on startle parameters (46,48-50), these demographic variables were introduced as covariates in analyses of covariance (ANCOVA). Based on significant main effects, Least Significant Difference (LSD) post-hoc comparisons were performed. Demographic frequency data were analyzed using Chi\(^2\)-tests. Interrelationships between startle measurements and clinical or demographic data were tested using Pearson’s product-moment-correlation. The confirmatory statistical comparisons were carried out at a significance level set at \( p<.05 \) (2-tailed). Within the correlation analyses, the significance level was set at \( p<.01 \) (2-tailed) in order to avoid accumulation of \( \alpha \)-error. Finally, effect sizes were calculated with *GPOWER* (51).
Results

Demographic data and clinical data

Demographic data and clinical data are shown in Table 1. Multiple and single comparisons with Chi²-tests revealed no significant differences with respect to gender and smoking, and ANOVA showed no significant differences with respect to years of education or verbal IQ between the groups. However, an ANOVA revealed a significant group effect for age [p<.01]. LSD post-hoc tests showed that both EP and LP were younger than US [p<.05] and MS [p<.01]. However, the mean age of HC did not differ from the other groups.

Although it was previously reported that age has an effect on startle magnitude and habituation, but not on PPI (49), we could not demonstrate any significant correlation between age and startle parameters within the total sample. Within subgroups, we found only a trend for correlations between PPI, startle reactivity and age in MS [r=-.55, p=.02; r=-.54, p=.02] indicating lower PPI and startle reactivity in older patients. However, we introduced age as a covariate in the analysis of startle data.

Analyses of the PANSS scores revealed significant group effects for all PANSS scores [p<.001]. LSD post-hoc tests revealed that EP had significantly lower positive [p<.01; p<.001], negative [p<.01], global [p<.05; p<.001], and total symptoms [p<.01; p<.001] than LP and US, whereas LP had significantly lower values in all of these scores than did US [p<.001]. Compared to US, the MS group showed significantly improved positive [p<.001], negative [p<.01], global [p<.001], and total symptoms [p<.001]. Furthermore, EP and LP showed significantly lower negative symptoms than did MS [p<.001; p<.05]. EP showed also a significantly lower total score than did MS [p<.01].

Analysis of the GAF scores revealed also a significant group effect [p<.001]. US had significantly worse psychosocial functioning than did EP, LP, and MS [p<.001]. Finally, MS exhibited a significantly better GAF score than did EP [p<.01].

****Insert Table I****
PPI

An ANCOVA (with age, gender, and smoking as covariates) revealed a significant group-effect with respect to %PPI \([F(4,105)=4.1, \ p<.01]\). LSD post-hoc tests showed that EP \([p<.01, \ d=.74]\), LP \([p<.01, \ d=.92]\), and US \([p<.05, \ d=.69]\) had a decreased PPI as compared to HC, whereas MS did not differ from HC \([p=.21, \ d=.38]\) (see Figure 1). The effects of age, smoking, and gender were not significant. Using a conservative clinical cut-off score, 26% of the EP, 37% of the LP, 36% of the US, and 18% of the MS had a PPI value lower than two standard deviations (SD) from the mean of the HC. When a one SD threshold is applied, 49% of the EP, 53% of LP, 50% of the US, and 30% of the MS did show abnormal PPI.

****Insert Figure 1****

Startle reactivity and habituation

An ANCOVA of the mean amplitude of pulse-alone trials (with age, gender, and smoking as covariates) showed that the groups significantly differed with respect to startle reactivity \([F(4,105)=2.5, \ p<.05]\). LSD post-hoc tests revealed a decreased startle amplitude in US compared to HC \([p=.05, \ d=.60]\). Moreover, US \([p<.01, \ d=.92]\) and LP \([p<.05, \ d=.61]\) showed a significant lower startle reactivity than did EP (see Figure 2). The effects of age, smoking, and gender did not reach significance level.

An ANCOVA (with age, gender, and smoking as covariates) of the linear gradient coefficient b did not show a significant group effect with respect to habituation \([F(4,105)=1.8, \ p=.13]\) (see Figure 3). The effects of the covariates were also not significant.

****Insert Figure 2****

****Insert Figure 3****

Exploratory analyses

An analysis of the ERiraos checklist at item level revealed that %PPI was significantly decreased in prodromal subjects reporting a history of perinatal complications (yes: 20.8%) \([F(1,52)=6.9, \ p<.01, \ d=.85]\), or in prodromal subjects showing thought-blocking (49%) \([F(1,52)=4.8, \ p<.05, \ d=.58]\),
delusion of jealousy (5.7%) \[F(1,52)=12.0, \ p<.001, \ d=1.87\], auditory hallucinations (5.7%) \[F(1,52)=11.0, \ p<.01, \ d=1.80\], olfactory and gustatory hallucinations (5.7%) \[F(1,52)=4.3, \ p<.05, \ d=1.20\], and somatic and tactile hallucinations (7.5%) \[F(1,52)=4.5, \ p<.05, \ d=1.07\] compared to prodromal subjects without those symptoms.

Previous studies reported different effects of typical and atypical antipsychotics on PPI (12,35,36,38,39). We therefore analyzed possible differences between the schizophrenia patients randomly treated with either haloperidol or risperidone (see Figure 4). In an ANOVA with the HC, the haloperidol-treated MS, and the risperidone-treated MS, there was a main group-effect on \%PPI \[F(2,42)=3.1, \ p<.05\]. Haloperidol-treated MS had a significant lower \%PPI as compared to HC \[p<.05, \ d=.89\]. Additionally, there was a trend for a lower \%PPI of the haloperidol treated MS compared to the risperidone-treated schizophrenia patients \[p<.07, \ d=.86\], whereas risperidone-treated subjects did not differ from HC \[p=.93, \ d=.04\]. There were no significant differences with respect to startle reactivity and habituation between haloperidol- and risperidone-treated MS.

During the follow-up observation period of 12 month, eight prodromal subjects (14.8%) transited into full-blown psychosis (three EP, five LP). Within the same period, two EP (5.7%) transited into the LP state. With respect to PPI, transited prodromal subjects (mean \%PPI: 36.0, SEM: ±7.7) did not differ from non-transited prodromal subjects (35.6±4.8). Both groups also did not differ with respect to startle reactivity and habituation.

****Insert Figure 4****

Correlations between startle measurement and clinical data

\%PPI, startle reactivity and habituation did not significantly correlate with verbal IQ, years of education, smoking, gender or psychopathological scales neither across all groups, nor within the groups.
Discussion

The present study is the first to investigate PPI, habituation and startle reactivity of the ASR in individuals fulfilling research diagnostic criteria of a psychotic prodrome. The major finding is that prodromal subjects had a significant PPI deficit. This was true for both early and late prodromal subgroups. As expected, we could also demonstrate reduced PPI in unmedicated first-episode schizophrenia patients, whereas medicated schizophrenia patients did not differ from controls. Further analysis revealed that the risperidone-treated patients had almost normal PPI, while the haloperidol-treated patients had a considerable attenuation of PPI.

These results strongly suggest that PPI deficits are present well before the onset of full-blown psychosis and that they are stable vulnerability-markers rather than state-dependent symptoms of schizophrenia. At first glance it may be somewhat surprising that the PPI deficit of prodromal subjects was comparable to that seen in unmedicated patients with first-episode schizophrenia because there are certainly some “false positives” within the prodromal group who will never proceed to psychosis. This could be explained by two reasons: First, about 15% of the prodromal subjects went on to develop psychosis during the brief 12-month follow-up interval but PPI scores of prodromal subjects subsequently transiting to psychosis did not differ from non-transited prodromal subjects. However, the expected long-term conversion rate of our prodromal subjects is much higher. Klosterkötter et al. have shown that 70% of the prodromal subjects, which were selected by similar criteria as the early prodromal subjects in the present study, transited to psychosis within 10 years (34). Long-term observations of ultra-high risk/late prodromal subjects are not available so far but the North American Prodrome Longitudinal Study (NAPLS) recently reported a transition rate of 35% within 2 ½ years (32). It is therefore premature to draw firm conclusions about the predictive validity of PPI because our follow-up period was too brief to detect all “true” prodromal subjects. Second, both the putative prodromal state and schizophrenia are characterized by information processing deficits and these deficits may be reflected by PPI reductions irrespective of later transition. The fact that PPI is markedly reduced in schizotypal personality disorder suggests that PPI is more related to symptoms of the schizophrenia spectrum in general rather than exclusively to full-blown psychosis (11,16). Thus,
we propose that PPI deficits capture an aspect of the trait-like vulnerability for psychosis, and this vulnerability can be inferred from family history, schizotypal or prodromal symptoms alike.

Moreover, the present data also validate the psychopathological approach for identifying high-risk subjects, given that a considerable proportion of the prodromal subjects with impaired PPI progressed to psychosis. The fact that high-risk subjects with an early prodrome also have a PPI deficits supports the inclusion of basic symptoms in recent European early detection studies (31,52).

For late prodromal subjects, a growing body of literature suggests that structural and functional brain alterations precede the onset of psychosis (53-55). Our finding of reduced PPI in late prodromal subjects is consistent with structural MRI findings of reduced grey matter volume in ultra-high-risk subjects for psychosis in several brain regions also implicated in PPI, i.e. hippocampus, basal ganglia, inferior frontal gyrus and superior temporal gyrus (56,57). Moreover, our data imply that early prodromal subjects already suffer from perturbation in the cortico-striato-pallido-thalamic (CSPT) circuitry which has been shown as responsible for processing PPI (17,58). In contrast, mediotemporal structural changes only became evident after the onset of a psychotic illness, which furthermore gave rise to the hypothesis that CSPT-changes occur prior to the onset of discernible mediotemporal lobe structural alterations (59).

In exploratory analyses, we found that PPI was particularly reduced in prodromal subjects reporting the negative symptom thought blocking or transient positive symptoms (BLIPS), especially delusion of jealousy or diverse types of hallucinations. This is in line with previous studies reporting that PPI deficits in schizophrenia are correlated with thought disorder (60-62) or with global scales of positive symptoms (63-65). The frequently replicated association of PPI with psychopathological symptoms of psychosis is consistent with the hypothesis that the impaired sensorimotor gating processes contribute to these symptoms (66). Interestingly, we also found that PPI was especially reduced in the prodromal subjects with suspected perinatal complications. This is in agreement with the finding that early developmental insults can contribute to the diathesis for schizophrenia (67). In addition, neurodevelopmental animal models of schizophrenia have shown that neonatal lesions of the hippocampus cause PPI disruption (68,69).
Although sample sizes were small, our present finding that only haloperidol-treated schizophrenia patients but not risperidone-treated patients showed a PPI deficit is in agreement with results of some earlier clinical studies (39,57). With respect to the underlying mechanisms, Kumari et al. concluded from their fMRI investigation that atypical substances maybe more effective in restoring activity in PPI-relevant regions than typical antipsychotics (57). Nevertheless, whether antipsychotic agents could reverse PPI deficits in schizophrenia is still subject of debate (35).

The present data illustrate a seeming discrepancy of two sets of PPI findings related to schizophrenia. First, the PPI deficit appears to be a stable trait marker, likely genetically influenced, and observed in high-risk populations such as family members or prodromal subjects. Second, PPI is a sensitive state marker of drug treatment in preclinical animal experiments and in several patient studies (as also shown here). This discrepancy is resolved when considering PPI to reflect the functional state of a basal sensorimotor gating system that may not be optimally “tuned” because of genetic or developmental reasons in schizophrenia. However, the function of this system can be normalized by (atypical) antipsychotics. Hence, PPI can be studied as an endophenotype to identify and characterize schizophrenia genes, but can also be investigated as a (state) biomarker of drug response.

In contrast to PPI, reduced startle reactivity seems to be an episodic indicator of psychosis, because we found that startle reactivity decreased progressively with increasing severity of symptoms, on an axis proceeding from early prodrome, through late prodrome, to full-blown psychosis. This finding is in line with our previous report that startle reactivity is significantly decreased in schizophrenia patients (15). Startle reactivity was improved by treatment with typical and atypical antipsychotics, in agreement with our previous report (15). Since there was no statistical significance between the haloperidol and risperidone group, this further indicates that different mechanisms underlie PPI and startle reactivity. Consistent with several previous findings, we did not find a significant habituation deficit in schizophrenia patients (8,11,12,39). Some of the discrepant reports regarding habituation deficits in schizophrenia might be due to subtle deficits in startle reactivity.
(13,47,60), which we found to be strongly correlated with habituation in the present sample \(r=-.59, p<.0001\) and in an earlier report of our laboratory (15).

The present study has some limitations. First, we have not assessed urine toxicology screenings in our participants. However, we consider it unlikely that undetected illegal substance use has influenced the results. Prodromal subjects turned to our hospital because of suffering from symptoms. Those reporting substance abuse were not included into the study but still received proper treatment, and thus prodromal subjects had no reason for deception. Second, in contrast to some previous studies (48,70), we did not detect an effect of smoking on PPI in our sample possibly for two reasons: a) Smoking withdrawal can decrease PPI (46,71), but our subjects were allowed to smoke ad libitum before testing. b) Especially heavy smokers with schizophrenia display higher PPI levels than light- or non-smoking patients (70) which is in line with the finding, that nicotine itself could enhance PPI (72,73). We did not assess severity of smoking behavior, and thus, the effect of smoking status alone was possibly too small to detect in our sample. Moreover, the criteria of the schizophrenia prodrome are still evolving. Our operational definitions for identification of subjects in a putatively prodromal state should not be taken as final even though the PPI data provide some neurobiological validation. Finally, on average, the prodromal subjects and the first-episode schizophrenia patients were older than in other studies probably for two reasons. First, administrative constrains required that all participants were 18 years or older. Thus, a large segment of the age distribution was cut. Second, it turned out that many prodromal subjects fulfilling the inclusion criteria were referred by secondary health care specialist, such as psychotherapists and psychiatrist, suggesting that they already suffered from symptoms already for a period of time. The observed age differences between prodromal subjects and schizophrenic patients are to be expected because the occurrence of prodromal symptoms precedes the first diagnosis of schizophrenia by several years (31).

Our study provides first evidence that a sensorimotor gating deficit is already present in the prodrome of schizophrenia, indicating that early attentional processes are defective prior to the transit to full-blown psychosis. The deficit was as pronounced as among first-episode schizophrenia patients.
In agreement with genetic high-risk studies, our results may indicate that impaired sensorimotor gating could serve as trait-marker of schizophrenia. If the present findings could be replicated, PPI assessment may validate and improve psychopathological risk assessment and early recognition of schizophrenia. The strategy of using experimentally-validated electrophysiological endophenotypes such as PPI or P50 suppression, and concomitant genetic analyses for research of subjects at high-risk could permit preclinical studies to better elucidate the neurobiological basis of risk of developing schizophrenia, and guide the testing of early intervention strategies with animal models (74). With respect to this aim, the homology of PPI across species presents an important advantage over other putative trait-markers of schizophrenia. Longitudinal assessment of prodromal individuals with sensorimotor gating paradigms should clarify the merit of these measures for reliable prediction of the onset of schizophrenia.
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**Figure legends**

**Figure 1:** Prepulse inhibition (PPI) of acoustic startle response of early prodromal subjects (EP), late prodromal subjects (LP), unmedicated first-episode schizophrenic patients (US), medicated first-episode schizophrenic patients (MS), and healthy control subjects (HC) (means and standard error of means). Prodromal subjects and unmedicated schizophrenic patients display a PPI deficit, whereas medicated schizophrenic patients showed improved PPI (LSD post-hoc tests (corrected for age, gender, and smoking): comparisons vs. HC: *p<.05, **p<.01).

**Figure 2:** Startle reactivity (mean amplitude of the first block of 116-dB pulse-alone trials) of early prodromal subjects (EP), late prodromal subjects (LP), unmedicated first-episode schizophrenic patients (US), medicated first-episode schizophrenic patients (MS), and healthy control subjects (HC) (means and standard error of means). Only unmedicated schizophrenic patients revealed significantly diminished startle reactivity. However, startle reactivity decreases with presumed increase of proximity to the onset of the illness within prodromal subjects (LSD post-hoc tests (corrected for age, gender, and smoking): comparisons vs. HC: *p<.05; comparisons vs. EP: #p<.05, ##p<.01).

**Figure 3:** Habituation of acoustic startle response (linear gradient coefficient b across six blocks of pulse alone trials) of early prodromal subjects (EP), late prodromal subjects (LP), unmedicated first-episode schizophrenic patients (US), medicated first-episode schizophrenic patients (MS), and healthy control subjects (HC) (means and standard error of means). Although US displayed lowered habituation, the groups did not significantly differ with respect to habituation.

**Figure 4:** Prepulse inhibition (PPI) of first-episode patients with schizophrenia who were randomly assigned to receive haloperidol (HAL) or risperidone (RISP) and healthy controls (HC) (means and standard error of means). Haloperidol treated patients still have a PPI deficit, whereas patients treated with risperidone showed normal levels of PPI compared to HC (LSD post-hoc tests: comparisons vs. HC: *p<.05; comparisons vs. RISP: †p=.07).
Table 1 Demographic and clinical characteristics of prodromal subjects, first-episode schizophrenic patients and healthy controls (means and standard deviation of means in parentheses; sex and smoking in frequency data).

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Prodromal subjects</th>
<th>First-episode schizophrenia patients</th>
<th></th>
<th>F/Chi²</th>
<th>df/df err</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(HC)</td>
<td>Early prodrome (EP)</td>
<td>Late prodome (LP)</td>
<td>Unmedicated (US)</td>
<td>Medicated (MS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>28</td>
<td>35</td>
<td>19</td>
<td>14</td>
<td>17</td>
<td>4/108</td>
<td>&lt;.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age</td>
<td>30.5 (10.6)</td>
<td>27.1 (6.6)</td>
<td>26.2 (8.3)</td>
<td>33.8 (8.5)</td>
<td>35.5 (12.4)</td>
<td>3.81 4/108</td>
<td>&lt;.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Men in percent</td>
<td>57.1</td>
<td>65.7</td>
<td>63.2</td>
<td>57.1</td>
<td>70.6</td>
<td>1.15 4</td>
<td>.89</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.3 (2.5)</td>
<td>15.6 (3.0)</td>
<td>14.7 (3.2)</td>
<td>14.8 (2.7)</td>
<td>13.8 (2.9)</td>
<td>1.33 4/108</td>
<td>.26</td>
</tr>
<tr>
<td>Estimated verbal IQ</td>
<td>105.7 (11.8)</td>
<td>105.3 (14.1)</td>
<td>102.6 (14.1)</td>
<td>105.2 (11.3)</td>
<td>110.5 (17.7)</td>
<td>1.10 4/108</td>
<td>.36</td>
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<tr>
<td>Smoker in percent</td>
<td>35.7</td>
<td>32.3</td>
<td>44.4</td>
<td>53.8</td>
<td>36.4</td>
<td>2.18 4</td>
<td>.70</td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>-</td>
<td>8.8 (2.0)</td>
<td>12.8 (4.3)</td>
<td>22.6 (7.9)</td>
<td>10.6 (3.7)</td>
<td>33.5 3/79</td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>-</td>
<td>9.8 (3.3)</td>
<td>15.1 (3.1)</td>
<td>24.4 (7.9)</td>
<td>18.9 (6.5)</td>
<td>29.4 3/79</td>
<td>&lt;.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>PANSS General</td>
<td>-</td>
<td>27.5 (6.6)</td>
<td>32.3 (5.7)</td>
<td>46.1 (11.7)</td>
<td>28.6 (8.7)</td>
<td>18.8 3/79</td>
<td>&lt;.001&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>PANSS Total</td>
<td>-</td>
<td>46.1 (8.4)</td>
<td>60.1 (11.2)</td>
<td>93.1 (24.8)</td>
<td>58.2 (17.0)</td>
<td>32.1 3/79</td>
<td>&lt;.001&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>GAF Score</td>
<td>-</td>
<td>57.0 (9.4)</td>
<td>60.2 (13.6)</td>
<td>34.9 (12.2)</td>
<td>66.2 (10.7)</td>
<td>13.2 3/79</td>
<td>&lt;.001&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> LSD post-hoc tests: MS > EP; p<.01; US > EP, LP; p<.05
<sup>b</sup> LSD post-hoc tests: US > EP, LP; p<.001; LP > EP; p<.01
<sup>c</sup> LSD post-hoc tests: EP < LP, MS; p<.001; LP < US; p<.001; LP < MS; p<.05; MS < US; p<.01
<sup>d</sup> LSD post-hoc tests: US > EP, LP, MS; p<.001; LP > EP; p<.05
<sup>e</sup> LSD post-hoc tests: US > EP, LP, MS; p<.001; EP < LP, MS; p<.01
<sup>f</sup> LSD post-hoc tests: US < EP, LP, MS; p<.001; EP < MS; p<.01
Prepulse Inhibition

**Figure 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>% PPI</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>HC</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>EP</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>LP</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>US</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>MS</td>
<td>10</td>
<td>17</td>
</tr>
</tbody>
</table>
Figure 2

Pulse alone trials, first block

HC
n=28

EP
n=35

LP
n=19

US
n=14

MS
n=17

arbitrary units
Figure 3

Habituation

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>28</td>
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<td>EP</td>
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<td>LP</td>
<td>19</td>
</tr>
<tr>
<td>US</td>
<td>14</td>
</tr>
<tr>
<td>MS</td>
<td>17</td>
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</tbody>
</table>

Linear gradient coefficient b
Figure 4

Prepulse Inhibition

<table>
<thead>
<tr>
<th>Group</th>
<th>% PPI</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td></td>
<td>28</td>
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<tr>
<td>HAL</td>
<td></td>
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<td>RISP</td>
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