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Lower prepulse inhibition in clinical high-risk groups but not in familial risk groups for psychosis compared with healthy controls

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Abstract

Aim: Although the lower level of prepulse inhibition (PPI) of the startle response is well known in schizophrenia, the onset of this difference is not clear. The aim of the present study was to compare PPI in individuals with clinical and familial high risk for psychosis, and healthy controls.

Methods: We studied PPI in individuals within three groups: ultra-high risk for psychosis (UHR, n = 29), familial high risk for psychosis (FHR, n = 24) and healthy controls (HC, n = 28). The FHR group was chosen among siblings of patients with schizophrenia, whereas UHR was defined based on the Comprehensive Assessment of At-Risk Mental States (CAARMS). We collected clinical data using the BPRS-E, SANS and SAPS when individuals with UHR were antipsychotic-naïve. A cognitive battery that assessed attention, cognitive flexibility, working memory, verbal learning and memory domains was applied to all participants.

Results: PPI was lower in the UHR group compared with both the FHR and HC groups. Those with a positive family history for schizophrenia had lower PPI than others in the UHR group. There was no difference in PPI between the FHR and HC groups. We found no relationship between PPI and cognitive performance in the three groups. Startle reactivity was not different among the three groups. Positive and negative symptoms were not related to PPI and startle reactivity in the UHR group.

Conclusions: Our findings suggest that clinical and familial high-risk groups for psychosis have different patterns of PPI.

KEYWORDS

clinical high risk for psychosis, cognition, familial risk for psychosis, prepulse inhibition

1 | INTRODUCTION

Prepulse inhibition (PPI) is a reduction of the startle reflex due to weak sensory prestimulation. It is a psychophysiologic index of sensorimotor gating. The majority of human studies measure orbicularis oculi muscle electromyographic activity of the blink reflex induced by acoustic stimuli. Impaired PPI in schizophrenia has been replicated in many studies and is regarded as an endophenotype for schizophrenia (Braff, Geyer, & Swerdlow, 2001; Braff & Light, 2005; Takahashi et al., 2011).

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In patients with psychotic disorders, deficits in sensorimotor gating may lead to cognitive fragmentation, disorganization, and psychotic symptoms. However, the stage at which this process is altered is unknown (Kapur, 2003). Deficits in PPI in subjects with schizophrenia have been related to cognitive impairments and psychotic symptoms (Kumari, Aasen, et al., 2008), and have been correlated with reductions in dorsolateral prefrontal, middle frontal, and orbital/medial prefrontal volume (Kumari, Antonova, & Geyer, 2008). PPI deficits have also been reported in people with schizotypal and psychosis-prone personality traits (Cadenhead, 2011; Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000; Kumari, Peters, et al., 2008; Swerdlow, Filion, Geyer, & Braff, 1995).

The heritability estimate for PPI was reported at rates ranging from 29% to 45% in different studies (Greenwood et al., 2007; Hasenkamp et al., 2010; Seidman et al., 2015). Individuals with familial risk for psychosis (ie, unaffected siblings of patients with schizophrenia) have been reported as having diminished PPI compared with controls (Cadenhead, 2005; Kumari, Das, Zachariah, Ettinger, & Sharma, 2005). However, there are some studies reporting no difference between siblings of patients with schizophrenia and healthy controls (Hasenkamp et al., 2010; Wynn et al., 2000).

Although the lower level of prepulse inhibition (PPI) of the startle response is well known in schizophrenia, it is not clear whether PPI deficit is present in those who have higher risk to develop psychosis. Findings from previous studies of PPI in people at ultra-high risk for psychosis (UHR) are inconsistent. Quednow et al. (2008), Ziermans, Schothorst, Magnee, van Engeland, and Kemner (2011), Ziermans et al. (2012), De Koning et al. (2014), and Winton-Brown et al. (2015) reported reduced levels of PPI in the aforementioned group. The latter study also found that PPI was particularly diminished in cannabis users from the UHR group. On the other hand, Cadenhead (2011) found no difference between the UHR and control groups. Biomarkers of clinical outcomes in this group are of particular interest because they may facilitate the stratification of high-risk samples according to the likelihood that an individual will subsequently develop psychosis or recover (Fusar-Poli et al., 2012).

It is important to rule out the effect of this confounder because the repairing effects of atypical antipsychotics on PPI have been reported in schizophrenia (Kumari, Fannon, Sumich, & Sharma, 2007; Wynn et al., 2007). As clinical high-risk groups are usually antipsychotic-naïve, studying PPI in these clinical and familial risk groups provides an advantage in understanding the nature of sensorimotor gating deficits. Another confounding source related to PPI is smoking and/or substance abuse (Jurado-Barba et al., 2011; Rabin, Sacco, & George, 2009).

PPI deficits are hypothesized to contribute to attention deficits and sensory overload, then resulting in cognitive deficits. However, studies that focus on the relationship between PPI and cognition in both patients with schizophrenia and healthy people have inconsistent results. PPI deficits were reported to be correlated with attention scores, working memory, verbal learning, and memory performances in both patient and control groups (Greenwood et al., 2015; Yang et al., 2017). In the recent Consortium of Genomics in Schizophrenia (COGS) study, it was reported that patients with schizophrenia with a higher PPI also had better working memory performances compared with those with a low PPI (Swerdlow et al., 2014). Additionally, Rabin et al. (2009) reported a relationship between PPI and executive functions only in smokers with schizophrenia. On the other hand, some other studies (Bitsios & Giakoumaki, 2005; Kishi et al., 2012; Swerdlow et al., 2006) found no relationship between PPI and cognition. To our knowledge, the relationship between PPI and cognition in individuals with UHR has not yet been studied.

The aim of the present study was to compare PPI in individuals with clinical and familial high risk for psychosis and healthy controls. We also analysed a possible relationship between PPI, and clinical and cognitive variables. We hypothesized that compared with controls, those with clinical and familial high-risk would have a lower PPI.

2 | METHODS

2.1 | Study sample

This cross-sectional study was conducted in the Psychotic Disorders Research Program, Istanbul University, Istanbul Faculty of Medicine. Our UHR sample comprised help-seeking individuals who came directly or were referred to our university clinic by other psychiatrists for further evaluation. Thirty-three individuals who were recently identified as being at UHR were consecutively recruited. UHR status was defined using the Comprehensive Assessment of At-Risk Mental States (CAARMS) interview (Yung et al., 2005). All CAARMS interviews were conducted by a senior psychiatrist (A.U.).

Thirty-two individuals met the criteria for attenuated psychosis, and one person met the Brief Limited Intermittent Psychotic Symptoms (BLIPS) criteria. Although our intention was to include individuals who met the criteria of both family history and functional deterioration, none of the referrals met both. All of the individuals with UHR were antipsychotic-naïve when they completed the cognitive battery and the sensorimotor gating task. Eight individuals were taking low-to-medium doses of selective serotonin reuptake inhibitors, and 16 were taking 1200 mg omega-3 fatty acid capsules, daily.

To homogenize the familial risk group, we included only the unaffected siblings of the patients with schizophrenia who were aged between 16 and 30 years as the FHR group (n = 26). Exclusion criteria for the control subjects included any major present or past diagnosis from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The healthy control group consisted of 33 people with no psychiatric symptoms, and without a first-degree relative with a psychotic disorder. The controls included local high school students and relatives of the hospital staff. The Structured Clinical Interview for DSM-IV, non-patient edition, sensorimotor gating task and neurocognitive battery were applied to the control group. All of the participants were of Caucasian origin.

We assessed clinical severity using the Brief Psychiatric Rating Scale-Extended (BPRS-E, Lukoff, Nuechterlein, & Ventura, 1986), SANS (Andreasen, 1983) and SAPS (Andreasen, 1984) in the UHR group. Although CAARMS measures the severity of disorders of

thought content, hallucinations, and formal thought disorder, we also applied the above-mentioned scales in order to obtain more detailed information about clinical symptoms.

All participants provided informed written consent for the study; informed consent was given by the parent if the participant was aged under 18 years. Exclusion criteria were the unwillingness to participate, illiteracy, the presence of a mental retardation diagnosis (previously identified), prior antipsychotic treatment, serious medical disease, prior history of psychosis that lasted more than a week, present alcohol and substance abuse. The protocol was reviewed and approved by the Ethics Committee of Istanbul Faculty of Medicine.

2.2 | Stimulus presentation

We screened the participants for hearing impairments (<45 dB 1000 Hz). The eye blink component of the acoustic startle response was measured by taking electromyography (EMG) recordings from the right orbicularis oculi in an acoustically isolated room during the morning. One 8-mm Ag cup electrode was placed on the outer canthus and another electrode was 1 mm medial of it over the right orbicularis oculi muscle. Auditory stimuli were given binaurally through stereo headphones. Participants were asked to look at a fixed red point on the screen during the task. The test began with a 2-minutes adaptation period of 60 dB SPL broadband background noise. In half of the 24 randomized trials, a prepulse preceded the startle stimuli, and other trials consisted of startle stimuli without a prepulse. There was a 70 dB background noise throughout the test. The prepulse and startle stimuli consisted of bursts of white noise. There was no prepulse in the first five trials and only a single stimulus of 115 dB with 40-ms duration was given. In the prepulse-stimuli couple, an 86-dB prepulse lasting 20 ms was given 120 milliseconds before the main stimuli.

The stimuli were presented in four blocks. In blocks 1 and 4, five 115-dB stimuli with 40 ms durations were presented. In blocks 2 and 3, 12 single stimuli and 12 prepulse-stimuli couples were presented randomly. Although 30 and 60-ms interstimuli intervals are also known to be used in psychosis groups, we chose 120-ms intervals instead, to match the parameters used by previous PPI studies in UHR groups (Quednow et al., 2008; Ziermans et al., 2011; Ziermans et al., 2012) and to enable a healthy comparison of findings. The mean inter-trial interval was 16 (range, 12 to 20) seconds. We examined two measures as startle reactivity and prepulse inhibition. Prepulse inhibition (PPI) was measured as the percent inhibition of the startle reflex in response to a weak prestimulus using a 120 ms prepulse interval (PPI% = 100 × (1 − [mean magnitude on prepulse trials/ mean magnitude on pulse alone trials])). Startle reactivity was calculated as the average of amplitudes of five responses in block 1. We used an EMG Brain Vision Recorder and Brain Vision Analyser for recording and analysing startle responses. None of the individuals smoked within an hour before recordings because they were in the laboratory. The total experiment time lasted approximately 15 minutes per person. We could not analyse the recordings of eight individuals (two FHR, two UHR and three HC) because of technical artefacts or nonresponses to stimuli. Two individuals in the UHR group did not complete the task because they could not follow the instructions due to attention problems. We analysed 29 individuals with UHR, 24 individuals with FHR, and 28 people in the HC group.

2.3 | Neuropsychological tests

Cognitive tests were chosen on the basis of their demonstrated reliability, ability to discriminate patients with psychosis from healthy participants, and lack of ceiling and floor effects in a UHR population. Performance measures that were selected for each cognitive test were the same as those selected for our previous studies which were conducted on individuals with UHR (Ucok et al., 2013; Ucok et al., 2015).

The Rey Auditory Verbal Learning Test is a list-learning task in which participants are read a list of unrelated words and are then tested for what they have learned by recall (Rey, 1964). Performance measures are the total number of correctly recalled words in trials I to V (verbal learning) in addition to the delayed recall trial (secondary verbal memory).

The Stroop Test measures selective attention, interference inhibition and processing speed as well as cognitive flexibility and executive function (Stroop, 1935). The number of commission errors and time difference between colour and word reading tasks provides the performance measures.

In the computer version of the Wisconsin Card Sorting Task (WCST), the participants are presented with the stimulus of cards with shapes on them. The dependent variables are the number of correct answers and sets completed. This test is used to measure executive function and working memory (Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

Continuous Performance Task (CPT) is used to measure sustained attention. Subjects perform a cued CPT in which they are given instructions to press a button only when the letter A is followed by the letter Z. The hit rate is used as the measure of sustained attention.

The Digit Span, a subtest from the Weschler Adult Intelligence Scale-Revised (WAIS-R, Weschler, 1987) measures short-term auditory recall. In the Digit Span Forward test, patients are asked to immediately repeat an increasing series of numbers read by the tester. In the Digit Span Backwards test, patients are asked to repeat the numbers in reverse order, in order to measure working memory capacity.

In Trail Making Test-A, 25 circles are numbered from 1 to 25 and participants are asked to draw lines to connect these numbers in ascending order. The test measures processing speed. In Trail Making Test-B, the circles include both numbers and letters. Participants are asked to connect the circles using both numbers and letters in ascending order (Reitan, 1955). These tests measure processing speed and working memory.

The N-back test is used to assess working memory function. Subjects performed the 2-back version of the task.

2.4 | Statistics

We tested all variables for normality with Kolmogorov-Smirnov tests. We used the Kruskal-Wallis test to compare PPI among the three groups because the number of participants in each group was smaller

than 30. When this comparison yielded a significant difference, we applied post-hoc analysis to compare couples using the Mann-Whitney *U* test. Additionally, the Spearman test was used to analyse the correlations between PPI and clinical and cognitive variables. Correlation analyses were repeated for men and women separately. All analyses were conducted using the SPSS version 16 statistics software (SPSS Inc., Chicago, Illinois). All tests of significance were two-tailed.

3 | RESULTS

The clinical and socio-demographic characteristics of the CHR, FHR, and control groups are presented in Table 1. There was no difference terms of sex, duration of education, age and smoking status of the participants.

3.1 | Prepulse Inhibition

PPI was found significantly different between the three groups (χ^2 = 9.91, df = 2, *P* = .007). We found that PPI was lower in the CHR group compared with both the familial risk group (*Z* = 2.49, *P* = .01) and healthy controls (*Z* = 3.08, *P* = .002) in our post-hoc analysis. There was no PPI difference between the familial risk group and healthy controls (*Z* = 0.137, *P* = .8). When we compared PPI among individuals in the UHR group (n = 12, eight individuals with first-degree relatives, four individuals with second-degree relatives) with and without family history (n = 17), we found that PPI was even lower in UHR individuals with a positive family history than those without a family history (26.2 ± 7.5 vs 44.2 ± 11.4, *Z* = 2.01, *P* = .04).

TABLE 1 Clinical characteristics, cognitive variables and sensorimotor gating findings of the study sample

	UHR, n = 29	FHR, n = 24	HC, n = 28
Age (years), mean (SD)	20.21 (4.49)	27.62 (5.24)	23.67 (6.11)
Male, n (%)	75.9	45.8	39.3
Education (years), mean (SD)	11.55 (2.55)	12.37 (3.51)	12.60 (3.73)
Smoking in last 6 months (%)	41.4	33.3	39.3
Number of cigarettes, mean (SD)	4.60 (6.99)	5.62 (8.25)	6.96 (9.27)
BPRS total score (SD)	45.2 (7.4)		
SAPS total score (SD)	18.8 (14.4)		
SANS total score (SD)	37.4 (19.04)		
WCST category, mean (SD)	5.67 (2.58)	6.41 (2.10)	7.21 (2.28)
WCST total error, mean (SD)	35.79(11.75)	37.9 (13.96)	32.5 (15.87)
Stroop test—word reading time, mean (SD)	29.96 (8.13)	30.12 (8.84)	25.07 (3.64)
Stroop test—Colour reading time, mean (SD)	69.5 (18.6)	74.7 (21.6)	57.9 (8.2)
Trail making A, mean (SD)	42.03 (16.05)	34.91 (11.35)	31.71 (10.57)
Trail making B, mean (SD)	1.06 (45.32)	1.05 (52.55)	80.07 (50.01)
PPI%, mean (SD)	17.8 (40.01)	46.00 (40.75)	48.62 (36.91)
Startle reactivity	32.9 (38.04)	36.8 (38.8)	35.7 (38.7)

3.2 | Impact of smoking and sex on PPI

First, we dichotomized each group as smokers and non-smokers. Although there was no difference on PPI in CHR and the FHR groups in terms of smoking status, PPI was higher in smokers in the healthy control group (*Z* = 2.17, *P* = 0.03). Then we analysed the relationship between daily cigarette consumption and PPI. The number of cigarettes consumed was not different between males and females in each group. There was no correlation between daily consumption and PPI.

Substance abuse was detected in one person in the FHR group and two individuals in the CHR group. None of the individuals in the control group had a history of substance abuse. We could not analyse the possible effects of substance abuse on PPI because the number of individuals with substance abuse was very low.

There was no sex difference on PPI in the CHR, FHR or control groups.

3.3 | The relationship between PPI and cognition and clinical variables

We selected 13 items from seven cognitive tests as performance parameters. None of them were correlated to PPI in any of the CHR, FHR and healthy control groups. Similarly, PPI was not found correlated to BPRS, SANS and SAPS total scores.

3.4 | Startle reactivity

There was no difference in pulse alone amplitude among the three groups. We found no relationship between startle magnitude and, daily cigarette consumption, positive, negative symptoms and cognitive performance. Startle reactivity was higher among women in the FHR group (*Z* = 2.01, *P* = .03); however, there was no sex difference in startle reactivity in the UHR and HC groups.

4 | DISCUSSION

We studied PPI in individuals with UHR for psychosis, the siblings of patients with schizophrenia and healthy controls. The findings partially supported our hypothesis. Although we found that PPI was lower in individuals with a clinical risk for psychosis compared with both those with familial risk and to controls, we found no difference between the familial risk group and controls. To the extent of our knowledge, this is the first study to compare PPI in clinical and familial risk groups. We

were also first to report findings on the relationship between PPI and cognition in risk groups for psychosis.

As PPI reflects the level of inhibitory function of the forebrain, our findings suggest that this dysfunction, which is shown in patients with schizophrenia, already exists in young people with clinical risk for psychosis. Our findings suggest that PPI deficits which were reported in patients with schizophrenia (Swerdlow & Light, 2018) begin in the earlier phases of the psychosis spectrum, as in line with the results of previous studies in UHR groups (De Koning et al., 2014; Quednow et al., 2008; Ziermans et al., 2011; Ziermans et al., 2012). We found that PPI in UHR was also lower than the FHR group. It seems that deficits in the above-mentioned circuits are not caused solely by the genetic load, but the contribution of some other factors which increase the risk of psychosis are also necessary. On the other hand, within the UHR group of our study, PPI was lower in individuals with a family history of schizophrenia compared to those without a family history. It can be speculated that genetic load increases sensorimotor gating deficits, which are already present in the UHR group.

As PPI is regarded among heritable endophenotypes for psychosis (Braff & Light, 2005), we expected that PPI in the FHR group would be lower than in the control group. Although the PPI levels of the FHR group were between the UHR group and healthy controls, we found no significant PPI difference between the unaffected siblings of patients with schizophrenia and the controls. Besides this, we found that PPI in the UHR group was lower than in the FHR group. It seems that having only a genetic load for psychosis is not enough to produce significant deficits in sensorimotor gating process. Another explanation is simply the relatively smaller sample size of the FHR group in our study. However, similar negative findings were reported from studies with larger numbers of relatives than our sample (Hasenkamp et al., 2010; Ivleva et al., 2014; Wynn et al., 2004), and lower PPI in relatives of patients with schizophrenia was reported from a study with even fewer siblings (n = 19) than ours (Kumari et al., 2005). We only used a 120-ms interstimuli interval in our task. In a previous study, significant heritability on PPI was reported only in trials using 60-ms interstimuli intervals, but not with 30 or 120-ms intervals (Hasenkamp et al., 2010). If 120-ms intervals are not suitable for reflecting the genetic component of PPI, our task paradigm might be involved in our negative findings when comparing FHR and HC groups.

We found no relationship between sensorimotor gating and cognitive performance in the UHR, FHR and HC groups. We cannot compare our study with its precedents because the relationship between PPI and cognition in UHR has not been studied previously. Our findings suggest that PPI deficits in the UHR group are either not directly related to cognition or its contribution was not robust enough to explain such a complex phenomenon as cognition. Again, the relatively small sample size of our study may have been responsible for our negative findings on the relationship between PPI and cognition.

We found no relationships between sensorimotor gating parameters and positive or negative symptoms, in accordance with findings of previous studies on UHR (De Koning et al., 2014; Quednow et al., 2008).

We also observed no intergroup differences in startle reactivity. This finding was in line with findings of previous studies (Cadenhead, 2011, Ziermans et al., 2012; Quednow et al., 2008; De Koning et al., 2014. Although Quednow et al. (2008) reported a negative relationship between startle reactivity and clinical severity in their prodromal group, we found no relationship between startle reactivity, and positive, negative symptoms and total BPRS score. Our findings are in line with De Koning et al. (2014) who found no relationship between startle reactivity and positive symptoms and overall clinical symptom level. Similar to previous reports (Cadenhead, 2011; Grillon et al., 2007; Quednow et al., 2008), we also found no relationship between smoking and startle reactivity.

The current study has several strengths. First, individuals with UHR were antipsychotic-naïve during the sensorimotor gating tasks and neurocognitive tests. This eliminated the effects of antipsychotics on PPI and cognition. Secondly, all participants were evaluated at the same study centre, and were ethnically homogenous. It is important to minimize discrepancies between different centres because significant inter-site differences on PPI were reported in a recent multi-site COGS study (Swerdlow et al., 2014). Third, neurocognitive performance was explored using several tests, which allowed us to evaluate the different domains of cognition.

Our study also has some limitations, however. We enrolled participants from a tertiary centre, which may limit the generalizability of our results because the participants were more likely to comprise help-seeking people. Additionally, we selected participants according to the CAARMS criteria, which focus more heavily on positive symptoms. This might have excluded individuals at UHR with predominantly negative symptoms. Moreover, the relatively small sample size may have been responsible for some of our negative findings as a result of a Type-II error. Although we analysed the effect of sex and tobacco separately, we could not look at these variables as part of an ANCOVA or MANOVA across all groups at the same time because of small sample size. We also did not assess startle latency which was found prolonged in individuals with psychosis. We could not analyse the relationship between baseline PPI deficits and conversion to psychosis, because of cross-sectional design of our study. Finally, as mentioned previously, we used only 120-ms inter-stimulus intervals in the sensorimotor gating task. This may also have limited the comparability of our findings with previous studies.

To summarize, in this cross-sectional study, we found that PPI was lower in individuals with ultra-high risk for psychosis compared with healthy controls and those with familial high risk. Our findings suggest that PPI deficits, which are reported in patients with schizophrenia, begin in the earlier phases of the psychosis spectrum. We might expect that early intervention programs targeting to reduce the conversion to psychosis might also help to minimize the sensorimotor gating deficits. Our next goal is to increase the sample size, and study the relationship between baseline PPI deficits and conversion to psychosis in a longitudinal study.

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