

# Prepulse Inhibition of the Startle Response in Men With Schizophrenia

## *Effects of Age of Onset of Illness, Symptoms, and Medication*

Veena Kumari, MA, PhD; William Soni, MB, BS, MSc; Vallakalil M. Mathew, MB, BS, MRCPsych; Tonmoy Sharma, MSc, MRCPsych

**Background:** Prepulse inhibition of the startle reflex response refers to the ability of a weak prestimulus to transiently inhibit the response to a closely following strong sensory stimulus. This effect represents an operational index of sensorimotor gating and is found to be deficient in schizophrenia. Prepulse inhibition deficits in schizophrenia seem to be partially normalized by typical antipsychotics and more fully by some atypical antipsychotics. Early onset of schizophrenia, particularly in men, has been associated with abnormal brain maturation, profound neuropsychological deficits, and less responsiveness to antipsychotic medication. We evaluated the effects of the age of onset of illness, current positive and negative symptoms, and the type of medication (typical vs atypical) on prepulse inhibition of the startle response in schizophrenia.

**Methods:** Thirty-eight male schizophrenic patients and 20 healthy male controls underwent testing for prepulse inhibition of the acoustic startle response.

**Results:** Earlier onset of illness was associated with reduced prepulse inhibition, while adult onset of illness was not. No significant relationships occurred between current symptoms and prepulse inhibition. Patients given typical, but not atypical, antipsychotics exhibited less prepulse inhibition compared with healthy controls.

**Conclusion:** Early onset of illness is associated with profound deficits in prepulse inhibition of the startle response in men with schizophrenia.

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**P**REPULSE inhibition (PPI) of the startle response represents an operational index of sensorimotor gating and is reliably demonstrable in both humans<sup>1</sup> and animals.<sup>2</sup> Prepulse inhibition provides a unique opportunity to characterize the attention and information processing deficits in schizophrenia that are core features of this illness.<sup>3</sup> It refers to a reduction in response to an intense, startling stimulus (the pulse) if this is preceded by 30 to 150 milliseconds by a nonstartling stimulus of subthreshold intensity (the prepulse).<sup>1</sup> The inhibitory mechanisms activated by the prepulse are thought to reduce the impact of any further stimulation until the processing of the prepulse is complete and thus prevent the organism from receiving an overload of information. In line with postulated deficits in early stages of information processing, several studies have demonstrated deficient PPI of the startle reflex in schizophrenic patients,<sup>4-6</sup> although some studies observed subnormal PPI in this population only when active attention to the prepulse was required.<sup>7,8</sup>

Individuals with an early onset of schizophrenia, predominantly men,<sup>9</sup> dis-

play a severe form of disease,<sup>10</sup> more structural brain abnormalities,<sup>11,12</sup> poor prognosis,<sup>10,13</sup> less favorable outcome with antipsychotic medication (especially with onset at age  $\leq 20$  years),<sup>14</sup> and poor neuropsychological functioning,<sup>15</sup> compared with those with a relatively later onset. The findings of greater PPI deficits in men than women with schizophrenia could also be because of their younger age at the onset of illness.<sup>16</sup> Numerous changes are thought to occur in the neuronal substrates for thought and behavior during adolescence, and the absence or failure of these maturational processes may lead to the onset of schizophrenia and associated cognitive abnormalities.<sup>17</sup> Furthermore, there is evidence for an association between earlier onset of illness and larger lenticular nuclei in schizophrenia<sup>18</sup>; PPI deficits in this population are thought to involve abnormalities of cortico-striato-pallido-thalamic circuitry, including lenticular structures.<sup>19</sup>

Recent studies have examined the relationship of deficient PPI with symptoms and other cognitive deficits in schizophrenia. Prepulse inhibition deficits have been found to be strongly associated with

From the Section of Cognitive Psychopharmacology, Division of Psychological Medicine, Institute of Psychiatry, University of London, London, England.

## SUBJECTS AND METHODS

### SUBJECTS

Forty-one male patients (age range, 20-59 years) with a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder were recruited from the inpatient and outpatient services at the Maudsley Hospital, London, England. All patients were diagnosed by an experienced psychiatrist using the Structured Clinical Interview for *DSM-IV*.<sup>32</sup> Of 41 patients recruited, 3 were excluded, either because of being nonresponders in reaction to startle probes ( $n=2$ ) or because there was no confirmation of the age of onset with documented records ( $n=1$ ). Thus, the final sample was composed of 38 patients.

Symptoms were rated on the day of testing using the Positive and Negative Syndrome Scale.<sup>33</sup> Age of onset was defined as the age at first appearance of psychotic symptoms (this definition has high reliability<sup>34</sup> and been used in previous studies<sup>9</sup>) as reported retrospectively by patients themselves, and confirmed by documented records in all cases.

All patients were receiving antipsychotics for a minimum of 6 weeks prior to their participation in the study. Ten patients had illness onset in adolescence<sup>18</sup> (age range, 13-20 years; 3 patients were given typical antipsychotics [2, fluphenazine decanoate and 1, zuclopenthixol]; 7 patients were given atypical antipsychotics [3, risperidone; 2, olanzapine; and 2, clozapine]; 5 patients [50%] were of low to lower-middle socioeconomic status as judged on the basis of parental occupation; and 5 [50%] were of upper-middle socioeconomic status). The remaining 28 patients had illness onset in adulthood (age range, 21-35 years; 6 patients were given typical antipsychotics [1, fluphenazine decanoate; 2, haloperidol; 1, chlorpromazine; and 2, flupenthixol]; 22 patients were given atypical antipsychotics [6, risperidone; 6, olanzapine; 9, clozapine; and 1, quetiapine]; 13 patients [46%] were of low to lower-middle socioeconomic status; and 15 patients [54%] were of upper-middle to upper socioeconomic status).

Twenty healthy male controls (age range, 20-50 years), screened for thyroid dysfunction; heart disease; hypotension or hypertension; a history of mental illness, anorexia, rapid mood changes, drug and alcohol abuse, or regular medical prescription; and presence of psychosis in their first-degree relatives, were recruited via advertisements in local newspapers and tested for comparison purposes. Healthy controls were paid for their time.

The study was approved by the Ethical Committee of the Institute of Psychiatry, London. All subjects gave their written informed consent.

### STARTLE RESPONSE MEASUREMENT

All subjects were tested for intact auditory abilities using an audiometer (Kamplex KLD23 Advanced Lightweight Diagnostic Audiometer; PC Werth Ltd, London) at 40 dB (A) (1000 Hz). No subject was excluded on this account. Startle testing was carried out using a commercial computerized human startle response monitoring system (Mark II; SRLab, San Diego, Calif). This was used to deliver acoustic startle stimuli, and record and score the electromyographic (EMG) activity for 250 milliseconds starting from the onset of the stimulus. Stimuli were presented to subjects binaurally through headphones (TDH39P; Telephonics, SRLabs, San Diego). Electromyographic recordings were taken with subjects sitting comfortably in a moderately lit soundproof laboratory.

Eyeblink component of the startle response was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, by positioning 2 miniature silver/silver chloride electrodes filled with Dracard electrolyte paste (SLE Ltd, Croydon, England). The ground electrode was attached behind the right ear on the mastoid.

The startle system recorded EMG activity for 250 milliseconds (sample interval, 1 millisecond) from the onset of the stimulus. The amplification gain control for the EMG

thought disorder in schizophrenia.<sup>20,21</sup> However, the relationship of PPI with some other cognitive abnormalities, such as poor performance on the Wisconsin Card Sorting Test, which correlates with tactile but not acoustic PPI,<sup>22,23</sup> and high distractibility on the continuous performance test,<sup>24</sup> and with both positive and negative symptoms of schizophrenia is rather weak.<sup>20,25,26</sup>

Pharmacological agents with psychotic and antipsychotic properties for humans, can disrupt and potentiate PPI in animals.<sup>27</sup> In the rat, the disruption of PPI by dopamine agonists is reversed by typical and atypical antipsychotics.<sup>27</sup> However, only atypical antipsychotics are able to antagonize the disruption of PPI that is caused by both serotonin and *N*-methyl-D-aspartate antagonists.<sup>27</sup> In line with the animal literature, there is a preliminary report that PPI may be reinstated by antidopaminergic medication in schizophrenia.<sup>28</sup> Importantly, a number of previous studies<sup>4-6</sup> reported PPI deficits in clinically stable patients, most of whom were on typical antipsychotics, which indicates, at best, partial rather than full restoration of PPI by typical antipsychotics. Prepulse inhibition deficits in schizophrenia seem to be

more fully normalized by the atypical antipsychotic clozapine.<sup>25,29</sup>

The main aim of this study was to address the hypothesis that earlier onset of illness would be associated with more impaired PPI in males with schizophrenia. The secondary aims were to examine the influence of current symptoms and medication (typical vs atypical) on PPI in schizophrenia. We hypothesised that there would be a greater degree of impairment of PPI in patients given typical antipsychotics than in those given atypical antipsychotics and healthy controls. Keeping in view the weak relationship between positive and negative symptoms of schizophrenia and PPI deficits, no strong prediction was made regarding the relationship of PPI with current symptoms. Given the previous findings of sex effects in PPI,<sup>30</sup> and hormonal effects on PPI in females,<sup>31</sup> the study sample was restricted to men. Although previous studies mostly used a 120-millisecond prepulse-to-pulse interval, we examined PPI at 3 different intervals, as varying prepulse-to-pulse intervals are thought to index different stages/processes of information processing,<sup>8</sup> and also found to interact with the pharmacological agents that affect PPI.<sup>25</sup>

signal was kept constant for all subjects. Recorded EMG activity was bandpass filtered, as recommended by the SRLab. A 50-Hz filter was used to eliminate the 50-Hz interference. Electromyographic data were scored off-line by the analytic program of this system for response amplitude using arbitrary analog-to-digit units (1 unit=2.62 mV) and latencies to response onset and peak (in milliseconds). Latency-to-response onset was defined by a shift of 6 digital units from the baseline value occurring within 18 to 100 milliseconds after the stimulus. The latency-to-response peak was determined as the point of maximal amplitude that occurred within 150 milliseconds from the acoustic stimulus. Responses (<5%) were rejected if the onset and peak latencies differed by more than 95 milliseconds or when the baseline values shifted by more than 90 units.

The session began with a 5-minute acclimatization period that consisted of 70 dB (A) continuous white noise. The pulse-alone stimulus was a 40-millisecond presentation of 115 dB (A) white noise; the prepulse stimulus was a 20-millisecond presentation of 85 dB (A) noise, both over 70 dB (A) of continuous background noise. Subjects received 61 startle stimuli. Sixty trials, in 5 blocks of 12 trials each, followed an initial pulse-alone trial. Each block consisted of 3 pulse-alone trials, 3 prepulse trials with a 30-millisecond prepulse-to-pulse interval, 3 prepulse trials with a 60-millisecond prepulse-to-pulse interval, and 3 prepulse trials with a 120-millisecond prepulse-to-pulse interval, presented to subjects in a pseudorandom order, with a mean intertrial interval of 15 seconds (range, 9-23 seconds).

Subjects were told that the experiment was to measure their attention to a number of auditory clicks, but no specific instructions were given as to attend or ignore them. They were told that "You are going to hear a number of auditory clicks, some of which may make you blink. Please keep your eyes open during this experiment which will last about 20 minutes." At the time of testing, the experimenter was aware of subjects' current age, but unaware of the specific diagnosis or any other clinical variables.

## STATISTICAL ANALYSIS

All analyses were performed using SPSS version 8.0 (SPSS Inc, Chicago, Ill). Prepulse inhibition was computed as the percentage of reduction of the amplitude over pulse-alone trials (ie,  $PPI = (ab)/a \times 100$ , where  $a$  indicates amplitude over pulse-alone trials and  $b$ , amplitude over prepulse trials. Such a procedure is recommended to correct for the influence of individual differences in startle amplitude.<sup>35</sup>

The relationship of PPI with the age of onset, positive and negative symptoms, general psychopathology, duration of illness, previous psychotic episodes, current age, and medication dose (calculated as chlorpromazine equivalents) was evaluated using Spearman rank order correlations.

The effects of age of illness onset were further examined using a 3 (group: adolescence onset, adult onset, and healthy controls)  $\times$  3 (trial type: prepulse trials with 30-millisecond, 60-millisecond, and 120-millisecond prepulse-to-pulse intervals) multivariate analysis of variance (MANOVA) (Wilks  $\lambda$ ) with repeated measures on trial type. A significant group effect was followed by lower-order MANOVAs. To examine the influence of age of illness onset on the amplitude and habituation of the response, the data over pulse-alone trials (excluding the first trial) were subjected to a 3 (group)  $\times$  5 (block: 5 blocks of 3 pulse-alone trials each) MANOVA, with block as a repeated-measure factor. The latencies to response onset and peak were (separately) examined by 3 (group)  $\times$  4 (trial type: pulse-alone and prepulse trials) MANOVAs.

The effects of medication type was analyzed by a 3 (group: patients given typical antipsychotics, patients given atypical antipsychotics, and healthy controls)  $\times$  3 (trial type) MANOVA. The effect of medication type (typical vs atypical) was further reevaluated after controlling for the age of illness onset using multivariate analysis of covariance. The influence of medication type on the amplitude and habituation of the response and the latencies to response onset and peak were analyzed similarly as described for the age of onset. The  $\alpha$  level for significance (2-tailed) was set at  $P < .05$ .

## RESULTS

### AGE OF ONSET

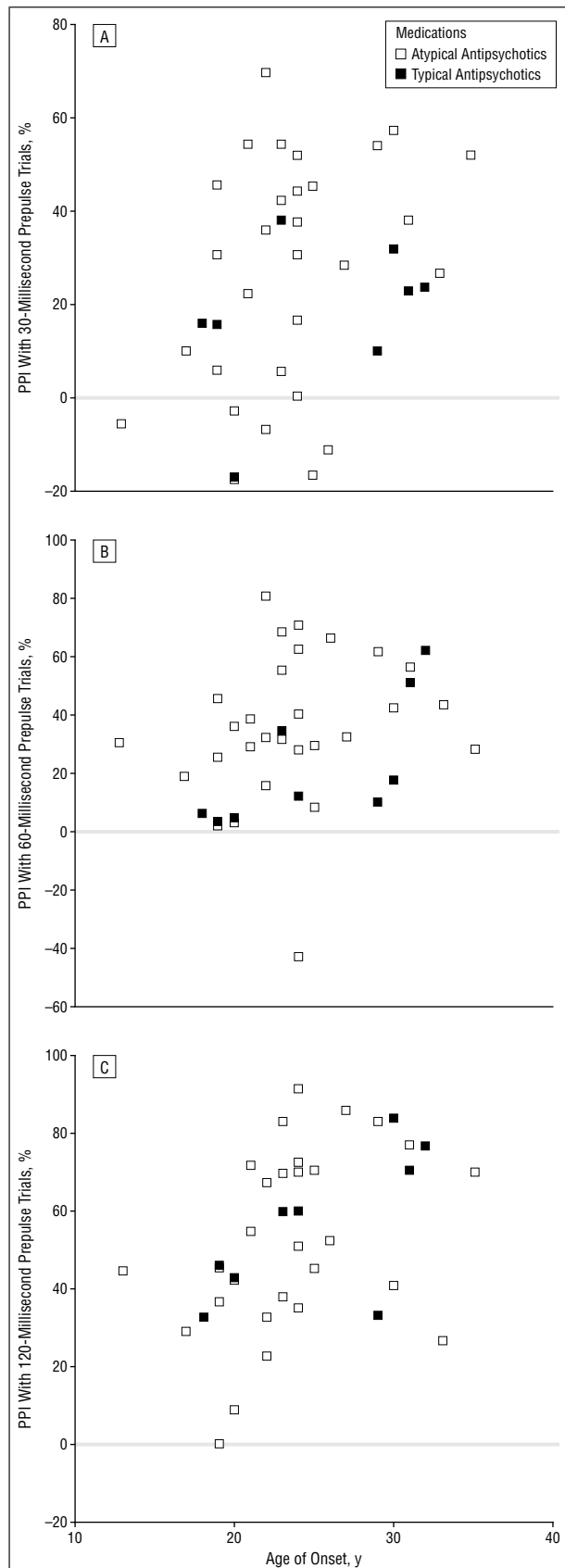
A positive relationship occurred between the age of illness onset and PPI with 120-millisecond ( $\rho_{38}=0.48$ ;  $P=.002$ ) and 60-millisecond prepulse trials ( $\rho_{38}=0.35$ ;  $P=.03$ ): the younger the patient at onset of illness, the lower the PPI. The relationship between PPI with 30-millisecond prepulse trials and the age of onset was also positive, although it failed to achieve formal significance ( $\rho_{38}=0.29$ ;  $P=.07$ ) (see **Figure 1** for scatterplots of PPI across the age of onset).

The age of illness onset was uncorrelated with the amplitude over pulse-alone trials ( $\rho_{38}=0.03$ ), positive symptoms ( $\rho_{38}=0.11$ ), general psychopathology ( $\rho_{38}=0.29$ ), number of previous episodes ( $\rho_{38}=-0.14$ ), duration of illness ( $\rho_{38}=0.24$ ), and the medication dose ( $\rho_{38}=-0.05$ ), but showed a positive relationship with negative symptoms ( $\rho_{38}=0.41$ ;  $P=.01$ ) (see the **Table** for the clinical characteristics of patients with adolescent and adult onset of illness).

The MANOVA to examine the influence of age of illness onset on PPI revealed a significant main effect of group ( $F_{2,55}=9.51$ ;  $P<.001$ ). There was reduced PPI in the adolescent-onset group ( $F_{1,28}=19.69$ ;  $P<.001$ ), but not in the adult-onset group ( $F_{1,46}=0.02$ ), as compared with healthy controls (see **Figure 2** for PPI with 30-millisecond, 60-millisecond, and 120-millisecond prepulses in all 3 groups). There was a significant main effect of trial type ( $F_{2,54}=34.08$ ;  $P<.001$ ), but no group  $\times$  trial type interaction ( $F_{4,106}=1.61$ ). No effects of age of illness onset were observed on response amplitude ( $F_{2,55}=1.11$ ) (adolescent onset: mean [SD], 516.21 [425.99]; adult onset: 355.41 [252.22]; controls: 456.35 [360.28]); habituation (group  $\times$  block:  $F_{8,104}=1.35$ ); or the latencies to response onset ( $F_{2,55}=1.45$ ) and peak ( $F_{2,55}=0.44$ ).

### SYMPTOMS

No significant relationships were found between PPI at any prepulse intervals and positive, negative, or disorganized symptoms. Also, no relationships occurred be-



**Figure 1.** Scatterplots of prepulse inhibition (PPI) scores with 30-millisecond (A), 60-millisecond (B), and 120-millisecond (C) prepulse trials across the age (in years) of onset in 38 male schizophrenic patients.

tween PPI and current age, general psychopathology, duration of illness, number of previous psychotic episodes, or the medication dose.

## MEDICATIONS

Patients given typical antipsychotics did not differ from those given atypical antipsychotics for the age of onset, current symptoms, number of previous psychotic episodes, duration of illness, or the medication dose, but were significantly older (Table). Age, as mentioned earlier, showed no relationship with PPI.

The overall 3 (group) × 3 (trial type) MANOVA revealed a group × trial type interaction ( $F_{4,106}=2.67$ ;  $P=.04$ ), which on further analysis showed that the patients given typical antipsychotics exhibited less PPI than healthy controls ( $F_{1,26}=4.10$ ;  $P=.05$ ), but only at short prepulse trials (group × trial type:  $F_{2,26}=6.19$ ;  $P=.006$ ). Also, PPI in patients on atypical antipsychotics did not differ significantly from either healthy controls ( $F_{1,47}=0.97$ ) or patients given typical antipsychotics ( $F_{1,36}=1.00$ ) (Figure 3). Multivariate analysis of covariance (MANCOVA) with the age of onset as a covariate showed improved but still non-significant differences between patients given typical and atypical antipsychotics ( $F_{1,35}=2.23$ ;  $P=.14$ ). However, the MANCOVA confirmed a strong effect of the age of onset on PPI ( $F_{1,35}=8.99$ ;  $P=.005$ ).

No effects of medication type were observed for response amplitude ( $F_{2,55}=0.44$ ) in patients given either typical antipsychotics (mean [SD], 443.62 [301.62] or atypical antipsychotics (352.45 [302.45]); in controls (456.35 [360.28]); for habituation (group × block:  $F_{8,104}=0.46$ ); and in the latencies to response onset ( $F_{2,55}=0.45$ ) and peak ( $F_{2,55}=1.93$ ).

## COMMENT

The most significant finding of this study supports our a priori hypothesis in showing that earlier onset of illness in male schizophrenic patients was associated with reduced PPI. Prepulse inhibition was unrelated to the current age, positive, negative, or disorganized symptoms, the duration of illness, the number of previous psychotic episodes, and the medication dose. Also as expected, patients given typical antipsychotics showed reduced PPI (though only at short prepulse intervals), as compared with healthy controls. However, patients given atypical antipsychotics did not show significantly greater PPI than those given typical antipsychotics. This may be because of the inclusion of patients receiving a range of atypical antipsychotics, all of which might not have been equally effective in normalizing PPI deficits. However, age of onset similarly influenced PPI in patients given typical antipsychotics and those given atypical antipsychotics.

This study is the first to report that the age of illness onset may be a moderating variable in disruption of PPI in schizophrenia. The simplest explanation is that this effect is caused by some disturbance at the neural level, because of onset of the disorder at a stage when the brain structures that mediate PPI were still maturing.<sup>17-19</sup> Early age of onset has also been associated with familial liability to develop schizophrenia<sup>34,36</sup> and obstet-

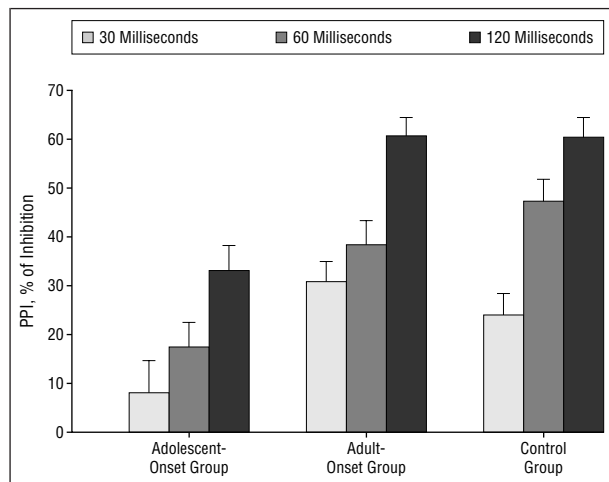
### Characteristics of Patients Classified by the Age of Onset of Illness and Medication Type\*

	Age of Onset of Illness, Mean (SD)		Medication Type, Mean (SD)	
	Early Onset (n = 10)	Adult Onset (n = 28)	Typical (n = 9)	Atypical (n = 29)
Age, y	34.30 (11.38)	37.68 (6.47)	42.44 (7.32)	35.03 (7.50) <sup>†</sup>
PANSS				
Positive symptoms	9.60 (2.46)	9.79 (3.24)	8.89 (1.62)	10.00 (3.32)
Negative symptoms	11.90 (4.12)	12.50 (4.85)	12.44 (3.32)	12.31 (5.01)
General psychopathology	24.50 (2.51)	25.54 (5.75)	24.56 (4.80)	25.48 (5.23)
Age at onset of illness, y	18.40 (2.12)	25.96 (3.98)	25.11 (5.49)	23.62 (4.75)
Duration of illness, y	15.90 (11.62)	11.71 (6.70)	17.33 (9.63)	11.41 (7.50)
No. of previous episodes	7.10 (6.26)	3.64 (2.41)	5.77 (4.66)	4.17 (3.81)
Medication dose, mg <sup>‡</sup>	552.16 (447.83)	540.78 (406.12)	432.27 (345.13)	578.26 (429.26)

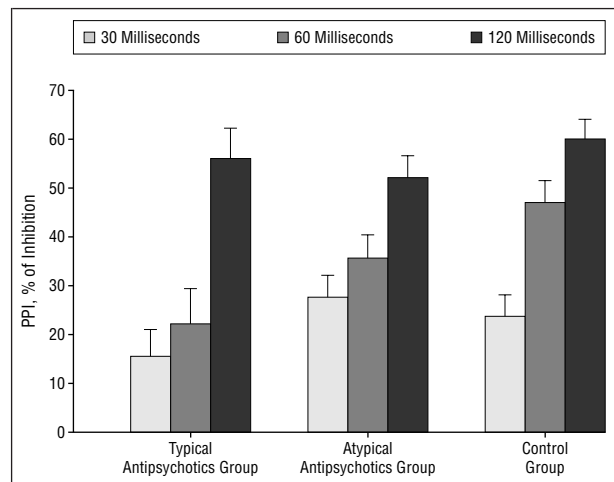
\*PANSS indicates Positive and Negative Syndrome Scale.

<sup>†</sup> $t_{36} = 2.60$ ;  $P = .01$ .

<sup>‡</sup>Measured in chlorpromazine equivalents.



**Figure 2.** Mean prepulse inhibition (PPI) (error bars, 1 SEM) of the startle reflex response by prepulse trials with 30-millisecond, 60-millisecond, and 120-millisecond prepulse-to-pulse intervals in patients with adolescent onset ( $n=10$ ) (adolescent-onset group) and adult onset of illness ( $n=28$ ) (adult-onset group), and healthy controls ( $n=20$ ) (control group).



**Figure 3.** Mean prepulse inhibition (PPI) (error bars, 1 SEM) of the startle reflex response by prepulse trials with 30-millisecond, 60-millisecond, and 120-millisecond prepulse-to-pulse intervals in patients given typical ( $n=9$ ) (typical antipsychotics group) and atypical antipsychotics ( $n=29$ ) (atypical antipsychotics group), and healthy controls ( $n=20$ ) (control group). Patients given typical antipsychotics showed less PPI than healthy controls with 60-millisecond prepulse trials ( $t_{27} = 2.98$ ;  $P = .006$ ).

ric complications,<sup>37</sup> which might be linked to disturbances at the neural level during neurodevelopment.<sup>38</sup>

The present findings suggest that in early-onset cases even atypical antipsychotics were not able to normalize PPI. Consistent with this possibility, there is evidence that atypical antipsychotics, such as clozapine, are less effective in early-onset patients, particularly in those who develop the illness at age 20 years or younger.<sup>39</sup> It has not yet been established which structural brain abnormalities associated with early-onset schizophrenia determine patients' responsiveness to medication. However, studies show that the severity of structural brain abnormalities at the onset of psychosis mediates individual variation in responsiveness to antipsychotics during patients' first episode of psychosis.<sup>40</sup> Early onset of illness also predicts poor responses to antipsychotics in patients with chronic schizophrenia.<sup>41</sup>

Previous studies have not specifically examined the effects of age of onset on deficient PPI, but a critical look at the literature reveals that in most studies<sup>4-6,24,25</sup> where PPI deficits were found, schizophrenic patients had, on average, illness onset at about age 23 years or younger,

which is lower than the average age of onset of patients who showed PPI within the normal range in this study. Unfortunately, no information on age of onset or duration of illness has been provided in some studies<sup>42,43</sup> that failed to find PPI deficits in passive paradigms.

Another important aspect of the present findings is that while PPI with 120-millisecond prepulse trials was most sensitive to age-of-onset effects, PPI with 60-millisecond prepulse trials produced the strongest difference between the patients given typical antipsychotics and healthy controls. Given that PPI with 120-millisecond prepulse trials is normalized by both typical and atypical drugs,<sup>25</sup> the strong effects of age of onset on PPI with 120-millisecond trials may indicate a failure in normalization of PPI with antipsychotics in those who developed the illness relatively early in life. Furthermore, differential effects of the age of onset and the type of medication on PPI at varying prepulse intervals, and no effects on other startle measures, support the notion that various startle characteristics tap different processes.<sup>8</sup>

## CONCLUSIONS

This study indicates that early onset of illness is associated with a profound disruption of PPI in men with schizophrenia. Prepulse inhibition of the acoustic startle may provide an objective experimental tool to investigate heterogeneity in illness and responsiveness to antipsychotics in schizophrenia. However, given the use of a cross-sectional design and the inclusion of patients who were given a number of atypical antipsychotics with different pharmacological profiles, this study is unable to provide conclusive evidence regarding possible normalization of PPI deficits in schizophrenia by typical and various atypical antipsychotics. Furthermore, this study lacked specific measures of thought disorder that consistently predict PPI deficits in schizophrenia,<sup>20,21</sup> and thus was not able to fully examine the relationship between PPI deficits and symptoms. Future longitudinal studies specifically aimed at examining the effects of various antipsychotics on PPI while taking into account patients' responsiveness to medication, age of onset, sex, and symptoms factors, with concurrent measurements of brain structures and functions in a larger sample, would be valuable in clarifying the present findings.

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Reprints: Tonmoy Sharma, MSc, MRCPsych, Section of Cognitive Psychopharmacology, Division of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, England (e-mail: t.sharma@iop.kcl.ac.uk).

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