



Sex differences in prepulse inhibition deficits in chronic schizophrenia

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Accepted 24 September 2003

Available online 29 November 2003

Abstract

Recent years have seen a dramatic growth in the number of studies using prepulse inhibition (PPI) paradigms to index information processing deficits in schizophrenia. There are, however, robust sex differences in PPI in healthy subjects, with women exhibiting less PPI than men in the absence of any psychopathology. To investigate the role of sex in prepulse modification deficits in the long-term course of schizophrenia, we assessed PPI (response inhibition with the prepulse preceding the pulse by 30–150 ms) and prepulse facilitation (PPF; response facilitation with the prepulse preceding the pulse by 1000 ms) of the acoustic startle response in 42 chronic schizophrenia patients (27 men; all 42 on typical antipsychotics) and 35 controls (15 men). The results revealed that healthy women showed less PPI than healthy men. Men with schizophrenia showed less PPI compared to healthy men, but women with schizophrenia did not differ in PPI from healthy women. Age of illness onset negatively correlated to PPI in male patients. There was no significant effect of sex in PPF, and although patients (regardless of sex) showed less PPF relative to controls, this effect was abolished when the current age was co-varied for. These findings indicate sex differences in PPI deficits in schizophrenia. Future studies of schizophrenia patients need to take sex and age of subjects into account to optimise the investigation of PPI deficits, and their clinical, neural, and pharmacological correlates. © 2003 Elsevier B.V. All rights reserved.

Keywords: Schizophrenia; Sex differences; Prepulse inhibition; Age of onset

1. Introduction

Prepulse inhibition (PPI) of the startle response (Graham, 1975) offers an objective and non-invasive tool to study information processing in experimental animals and human subjects in parallel investigations.

PPI refers to the ability of a weak prestimulus (prepulse) to transiently inhibit the response to a closely following (by 30–500 ms) strong sensory stimulus (pulse). However, if the time interval between the prepulse and pulse is longer (500–2000 ms), then a facilitation, rather than reduction, is seen (Graham and Murray, 1977). This phenomenon is known as prepulse facilitation (PPF). PPI is thought to reflect reduced processing of incoming information while processing of the initial stimulus (prepulse) is still

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ongoing (Hoffman and Searle, 1968). This has led to the suggestion that PPI is an information processing mechanism reflecting sensorimotor gating that protects the individual from sensory overload (Braff and Geyer, 1990). PPF with long lead (prepulse-to-pulse) intervals is proposed, at least in part, to reflect sensory enhancement linked with modality-specific selective attention (Anthony, 1985).

Sex differences in PPI of the startle response in healthy populations, with women exhibiting less PPI than men, have been observed in several studies (Blumenthal and Gescheider, 1987; Ornitz et al., 1991; Swerdlow et al., 1993, 1995, 1997, 1999; Abel et al., 1998; Kumari et al., 2003; all studies tested subjects under passive conditions, i.e. no specific instructions to attend to the prepulse; see Appendix A1). Although a pharmacological study (Della Casa et al., 1998) suggested sex differences in human PPI to be moderated by smoking status of the subjects, Swerdlow et al. (1999) have shown, with retrospective analysis involving >600 subjects of both sexes, that sex differences in PPI are robustly present in studies when women are tested without regard to where they are in the menstrual cycle and is not explained by a difference in cigarette smoking status (Swerdlow et al., 1999). There is evidence (Swerdlow et al., 1997) to suggest that PPI in women varies across the menstrual cycle, with maximum PPI occurring 1–7 days after the last (self-reported) menstrual period, but healthy women show less PPI than men even when tested during the early follicular phase (days 1–7) of the menstrual cycle (Abel et al., 1998; Kumari et al., 2003; see Appendix A1). There is no direct evidence so far of a sex difference in PPF in healthy human populations (Ornitz et al., 1991; Appendix A1).

Consistent with Graham's (1975) suggestion that PPI may provide a sensitive measure of sensorimotor gating deficits in schizophrenia, and thus increase the understanding of the well documented deficiency of schizophrenia patients to efficiently process rapidly presented sensory information, reduced PPI has repeatedly been observed in patients with schizophrenia (e.g. Braff et al., 1978, 1992, 2001a; Grillon et al., 1992; Cadenhead et al., 2000; Parwani et al., 2000; Perry et al., 2002; Mackeprang et al., 2002; Duncan et al., 2003; Ludewig et al., 2003a). These deficits are more reliably seen in unmedicated patients or those treated with typical antipsychotics, since some recent

studies (Kumari et al., 1999, 2000, 2002; Leumann et al., 2002; Oranje et al., 2002) have reported that patients treated with atypical antipsychotics (likely to have responded well to a particular atypical antipsychotic in the longer term having been through other, perhaps less successful, antipsychotic treatments) show normalized PPI or have less severe deficits relative to those treated with typical antipsychotics. PPI in this patient population is found to negatively correlate with the severity of thought disorder (Perry and Braff, 1994; Perry et al., 1999) and also with distractibility on the Continuous Performance Test (Karper et al., 1996). A modest negative relationship between PPI and symptoms (i.e. high levels of both negative and positive symptoms predict poor PPI; Braff et al., 1999; Ludewig and Vollenweider, 2002), and a positive relationship between PPI and the age at illness onset (i.e. earlier onset associated with more severe disruption; Kumari et al., 2000) has also been observed in schizophrenia. Other data (Weike et al., 2000) suggest that effective treatment of symptoms improves PPI in this patient population, though other studies (Mackeprang et al., 2002; Duncan et al., 2003), while replicating the observation of deficient PPI in patients relative to controls, did not find a co-variation between PPI and symptom improvement with antipsychotic treatments. Although in some studies, which used rather intense prepulses (i.e. about 25 dB above the background) and required the subjects to 'attend' or 'ignore' the prepulse on certain trials, deficient PPI was seen only under the 'attend' condition (Dawson et al., 1993; Hazlett et al., 1998) or seen when assessed with P2 component of the event related potentials, but not when assessed with the amplitude of the acoustic eye blink response (Ford et al., 1999; 10/15 patients on atypical antipsychotics), there seems to be consistent evidence for deficient PPI of the acoustic eye blink startle response, recorded electromyographically in passive paradigms elicited with discrete prepulses (of 2–16 dB above the background), especially in unmedicated patients and those treated with typical antipsychotics (review, Braff et al., 2001b; Kumari and Sharma, 2002). This deficit, as proposed by Braff et al. (1999), may correlate more strongly with cognitive abnormalities and thought disorder than with schizophrenic symptoms.

PPF (passive) has not been as widely investigated as PPI in schizophrenia, with relatively fewer studies

employing both PPI as well as PPF measurements (Braff et al., 1978; Bolino et al., 1994; Ford et al., 1999; Leumann et al., 2002; Ludewig and Vollenweider, 2002). PPF deficits in schizophrenia have also been a less consistent finding than the PPI deficits. PPF deficits were found to be present in a sub-sample of schizophrenia patients in one of the two recent studies from the same research group that used discrete acoustic prepulses to elicit PPI/PPF (no PPF deficit, Leumann et al., 2002; reduced PPF in schizophrenia patients with deficit syndrome, Ludewig and Vollenweider, 2002) but not in two other studies which used a continuous acoustic prepulse (Braff et al., 1978) or an electrical prepulse (Bolino et al., 1994). Ford et al. (1999) reported PPF deficits assessed with N1 component of the event related potentials, but not when assessed with the amplitude of the acoustic eye blink response.

Interestingly, there are sex differences not only in PPI in healthy human subjects (Appendix A1) but also in the clinical presentation of schizophrenia (Lewine, 1981; Castle and Murray, 1991; Andia et al., 1995) with men, on average, displaying an earlier age of onset (Faraone et al., 1994; until menopause in women, Hafner, 2003) and a poor treatment response (Jonsson and Nyman, 1991) especially in relation to the earlier age of onset in the long-term chronic course of the disorder (Meltzer et al., 1997; Smith et al., 1998). Given the sex differences, noted earlier, in PPI in healthy subjects, and the associations of an earlier age of illness onset to reduced PPI (Kumari et al., 2000), the male sex (Faraone et al., 1994), and reduced responsiveness to antipsychotic medication (Smith et al., 1998), it is possible that there are sex differences in PPI deficits in the long-term chronic course of this illness.

Previous studies of PPI that included schizophrenia patients of both sexes and also included a control group of healthy subjects of both sexes (Braff et al., 1978, 1992, 2001a; Dawson et al., 1993; Bolino et al., 1994; Hazlett et al., 1998; Cadenhead et al., 2000; Weike et al., 2000; Leumann et al., 2002; Ludewig and Vollenweider, 2002; Oranje et al., 2002; Perry et al., 2002; Mackeprang et al., 2002; see Appendix A2 for details) did not specifically focus on examining sex effects. Other PPI studies of schizophrenia patients (Braff et al., 1999; Kumari et al., 1999, 2000, 2002; Ford et al., 1999; Parwani et

al., 2000; Duncan et al., 2003; Ludewig et al., 2003a) restricted their samples to men only. The only published report to have considered the role of sex in PPI deficits in schizophrenia is by Swerdlow et al. (1993). They (Swerdlow et al., 1993) provided post-hoc analyses of data in 22 patients and 25 controls included in an earlier study by Braff et al. (1992) (sex distribution not provided in either Braff et al., 1992 or Swerdlow et al., 1993) and reported (a) a significant effect of diagnosis (PPI in patients < controls), (b) no effect of sex, and (c) no sex \times disease interaction. It is interesting that although the authors did not find a sex \times disease interaction, they also did not find a significant sex effect for the combined (patients and controls) sample. This can be taken to suggest that the sex effect in PPI (men > women) in controls was absent (if not reversed) in the schizophrenia group and therefore the effect of sex in PPI seen in controls was destroyed in the combined (patients and controls) sample, instead of becoming stronger with a larger sample.

This study aimed to examine the role of sex in PPI in patients with chronic schizophrenia, taking into account their age at the onset of illness and current symptoms, controlling for medication status as much as possible (i.e. all patients stable on typical antipsychotics) and using stimulus parameters (i.e. discrete prepulse stimulus, 15 dB above the background, in a passive paradigm) that most strongly differentiate schizophrenia patients from healthy controls (Braff et al., 2001a) and also reveal sex differences in PPI in healthy subjects (Swerdlow et al., 1993, 1995, 1997, 1999; Abel et al., 1998; Kumari et al., 2003). Given the consistent reports of sex differences in PPI, but not in PPF, in healthy subjects, and of reliable PPI deficits, but not PPF deficits, our main focus was on investigating the possibility of varying degree of deficits in PPI in men and women with schizophrenia. We, however, also included the assessment of PPF albeit with reduced power (see Section 2.3). On the basis of previous observations, we hypothesized that patients with schizophrenia, as a group, will show reduced PPI, relative to the group of healthy controls. We further hypothesized that men with schizophrenia will display reduced PPI, compared to healthy men, but women with schizophrenia might not show significantly reduced PPI,

relative to healthy women who themselves were hypothesized to show less PPI than healthy men. We expected, though with limited confidence, to find PPF deficits in both men and women with schizophrenia, and adopted an exploratory approach for the investigation of sex effects in PPF in controls as well as patients with schizophrenia.

2. Methods

2.1. Subjects

Forty-two patients (27 men, 15 women; age-range 21–65 years) with a DSM-IV diagnosis of schizophrenia, diagnosed by a research psychiatrist using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) recruited from the inpatient and outpatient services within and around London took part. All patients were stable on a range of typical antipsychotics for a minimum of 6 weeks prior to their participation in the study. In addition to antipsychotics, 11 patients (eight men and three women) were receiving anticholinergic medication and two male patients were taking antidepressants. Symptoms were rated within 4 days of testing using the Positive and Negative Syndrome scale (PANSS) (Kay et al., 1987). Age of onset was defined as age at first appearance of psychotic symptoms (this definition has high reliability; Kendler et al., 1987, and has been used in previous studies; Faraone et al., 1994) as reported retrospectively by patients themselves, and confirmed by documented records in all cases. Reliable information regarding age of illness onset (one female and one male) and number of previous episodes (two male) could not be established for some patients, and these patients were therefore not included in the analysis involving these factors. Thirty (20 men and 10 women) of 42 patients were regular cigarette smokers with, on average, considerable dependence on nicotine as assessed by their Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom, 1978) scores (men: mean = 5.50, S.D. = 2.80; women: mean = 4.60, S.D. = 2.21). Five of the 15 women were post-menopausal. There were no pregnant or lactating women. See Table 1 for clinical characteristics of patients with schizophrenia.

Table 1

Clinical characteristics of patients with schizophrenia

	Women mean (S.D.)	Men mean (S.D.)
Age (in years)	45.93 (12.56)	43.22 (10.29)
^a Positive symptoms*	12.33 (5.23)	19.30 (7.67)
Negative symptoms	17.60 (6.86)	18.67 (5.36)
^b General psychopathology*	33.20 (9.87)	39.52 (10.39)
Age at onset of illness	24.86 (10.94)	25.11 (7.09)
Duration of illness	20.07 (12.61)	17.42 (11.91)
Number of previous psychotic episodes	4.93 (4.92)	3.96 (3.15)
^c Medication dose (expressed as chlorpromazine equivalents in mg)*	122.05 (70.33)	266.01 (246.24)

* Higher in men: ^a $t=3.13$, $df=40$, $p=0.003$; ^b $t=1.92$, $df=40$, $p=0.06$; ^c $t=2.20$, $df=40$, $p=0.03$.

Thirty-five healthy subjects (15 men, 20 women; age-range 20–65 years), screened for a history of mental illness (screened with SCID-NP) (First et al., 1996), anorexia, rapid mood changes, drug and alcohol abuse, regular medical prescription and presence of psychosis in their first degree relatives, were recruited via advertisements in local newspapers and tested for comparison purposes. Nine (four men and five women) of 35 healthy subjects were regular cigarette smokers (mean FTQ scores for men = 5.00, S.D. = 0; for women, mean = 3.80, S.D. = 1.64). One woman was post-menopausal. Healthy subjects were paid for their time.

The study procedures were approved by the Ethical Committee of the Institute of Psychiatry, London. All subjects gave their written informed consent after the study procedures had been fully explained to them.

2.2. Startle response measurement

All included subjects were screened for intact auditory abilities using an audiometer (Kamplex, AS7) at 40 dB [A] (1000 Hz). Startle testing was carried out using a commercial computerized human startle response monitoring system (Mark II, SR-Lab, San Diego, CA). The same system delivered acoustic startle stimuli, and recorded and scored the electromyographic (EMG) activity for 250 ms starting from the onset of the stimulus. Stimuli were presented to subjects binaurally through headphones (Telephonics, TDH-39P). EMG recordings were obtained with sub-

jects sitting comfortably in a moderately lit sound-proof laboratory.

The eye blink component of the startle response was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, by positioning two miniature silver/silver chloride electrodes filled with Dracard electrolyte paste (SLE, Croydon). The ground electrode was attached behind the right ear on the mastoid. The startle system recorded EMG activity for 250 ms (sample interval 1 ms) from the onset of the pulse stimulus. The amplification gain control for EMG signal was kept constant for all subjects. Recorded EMG activity was band-pass filtered, as recommended by the SR-Lab. A 50-Hz filter was used to eliminate the 50-Hz interference. EMG data were scored off-line blind to group allocation using the analytic program of this system for response amplitude (in arbitrary Analog-to-Digit units; 1 unit=2.62 μ V), and latencies to response peak (in ms). The latency to response peak was determined as the point of maximal amplitude that occurred within 150 ms from the acoustic stimulus. Responses (<5%) were rejected when the baseline values shifted by more than 50 digital units.

Three patients (two men and one woman) and one healthy male subject had to be excluded (these subjects were in addition to the 42 patients and 35 controls reported in this paper) because of poor startle data quality or data acquisition problems. Specifically two schizophrenia patients did not provide sufficient useful data in the last two blocks of the experiment (>40% non-startle trials), one female patient had a very noisy baseline, and one male control was defined as a startle non-responder (averaged response amplitude less than 25 units over the first block of pulse-alone trials).

2.3. Experimental paradigm and procedure

The pulse-alone stimulus was a 40-ms presentation of 115-dB (A) white noise and the prepulse stimulus a 20-ms presentation of 85-dB (A) noise, both over 70-dB (A) continuous background noise. The session began with a 5-min acclimatization period consisting of 70-dB (A) continuous white noise. Subjects received 85 startle stimuli in all. Eighty-four trials, in four blocks of 21 trials each, followed an initial pulse-alone trial. Each block consisted of three pulse-alone trials, three prepulse trials with a 30-ms prepulse-to-

pulse (onset to onset) interval, three prepulse trials with a 60-ms prepulse-to-pulse interval, three prepulse trials with a 90-ms prepulse-to-pulse interval, three prepulse trials with a 120-ms prepulse-to-pulse interval, three prepulse trials with a 150-ms prepulse-to-pulse interval, and three prepulse trials with a 1000-ms prepulse-to-pulse interval presented to subjects in a pseudorandom order with a mean inter-trial-interval of 15 s (range 9–23). Prepulse trials with a 1000-ms prepulse-to-pulse interval were expected to elicit PPF; all other prepulse trials were expected to elicit PPI. As noted in the Introduction, our main focus was on PPI, but we also included one prepulse-to-pulse interval to explore sex and disease effects in PPF. We used a 1000-ms prepulse-to-pulse interval for this purpose to avoid masking of possible sex differences by possible ceiling effects with longer prepulse-to-pulse intervals (i.e. likely to elicit stronger PPF). The session lasted about 30 min.

Subjects were told that the experiment measured 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 30 min”. At the time of testing, the experimenter was aware of their current age, but unaware of the diagnosis or any other clinical data. There was no explicit restriction on smoking intake prior to testing but care was taken not to take subjects to the startle laboratory for about 25 min after they had a cigarette, in order to prevent a state of smoking withdrawal or a heavy intake during the testing session. The effect of menstrual cycle phases was not examined in this study since antipsychotic medication makes it difficult to infer hormonal status in women with schizophrenia in absence of direct hormonal assessments (Canuso et al., 2002). Furthermore, healthy women have less PPI than men even when tested during the first 10 days of the menstrual cycle (Abel et al., 1998), although they show the highest level of PPI during this time (Swedlow et al., 1997).

2.4. Data analysis

Prepulse modification on trials where a prepulse preceded the pulse was computed as percentage

reduction of the amplitude over pulse-alone trials, i.e. prepulse modification= $([a - b])/a \times 100$, where a =amplitude over pulse-alone trials, and b =amplitude over prepulse trials. This procedure was adopted to correct for the influence of individual differences in startle amplitude (Mansbach et al., 1988).

Firstly, the effect of diagnosis and sex in amplitude and habituation of the response over the pulse-alone trials were examined using a 2 (Group: patients, controls) \times 2 (Sex: male, female) \times 4 (Block: four blocks each with three pulse-alone trials) multivariate analysis of covariance (MANCOVA; Wilks' F) with Block as a within-subjects factor, Group and Sex as between-subjects factors, and age as a covariate. Age was used as a covariate given very recent observations (Ellwanger et al., 2003) of significant age effects in amplitude (decreases with age), latency (increases with age) and PPI (inverted-U type relationship) of the acoustic startle response in healthy human subjects. Significant interactions were followed by lower order MANCOVAs and the analysis of simple main effects as appropriate. The relationship of pulse-alone amplitude to the dose of antipsychotic medication, expressed as chlorpromazine equivalents, in patients was examined using Spearman rank order correlations. Following the observations of (a) a negative relationship between the dose of antipsychotic medication and pulse-alone amplitude (see Results) and (b) higher medication dose in men compared to women with schizophrenia (Table 1), the difference between women with schizophrenia in response amplitude (see Results) was further examined with Sex \times Block MANCOVA, with the dose of medication entered as a covariate.

Next, the effects of diagnosis and sex in PPI were evaluated with a 2 (Group) \times 2 (Sex) \times 5 (Trial Type: PPI with 30-, 60-, 90-, 120- and 150-ms prepulse-to-pulse interval trials) \times 4 (Block; PPI calculated separately for the four blocks described in the experimental paradigm) MANOVA with Trial Type and Block as within-subjects factors and Group and Sex as between-subjects factors. These effects were re-evaluated using a MANCOVA with the amplitude over the pulse-alone trials and age entered as covariates. Age was entered as a covariate, keeping in view the observations of Ellwanger et al. (2003), and pulse-alone amplitude was entered as a covariate because it was affected by a significant

Group \times Sex interaction (see Results) and thus might have influenced Group \times Sex effects in PPI. A significant Group \times Sex interaction was followed by further MANCOVAs (a) to examine Group (i.e. patients versus controls) effects separately in men and women, and (b) to examine whether difference in PPI between men and women within the patient group (see Results) was explained by clinical variables, namely, age at the onset of illness, number of previous episodes, positive symptoms, negative symptom, or general psychopathology (these variables were entered as covariates, in addition to age and amplitude over pulse-alone trials in this analysis). The effects of smoking status (smoker versus non-smoker male and female patients) and anticholinergic use (those receiving anticholinergic medication versus not receiving; this analysis restricted to male patients only; see Section 2.1) on PPI were also investigated by appropriate MANCOVAs after co-varying for age and pulse-alone amplitude. Finally, PPI in women with schizophrenia was assessed to examine the effects of menopause (i.e. PPI in 10 menstruating versus five post-menopausal women) with pulse-alone amplitude entered as a covariate.

The effects of diagnosis and sex in PPF were initially evaluated with a 2 (Group) \times 2 (Sex) \times 4 (Block) MANOVA with Block as a within-subjects factor and Group and Sex as between-subjects factors. The effects of diagnosis and sex in PPF were also re-evaluated by MANCOVAs with the amplitude over the pulse-alone trials, age and relevant clinical variables (as for PPI) entered as covariates, following a similar procedure described earlier for PPI. The PPF data were analysed separately to PPI because PPF would be expressed as a negative value, as opposed to PPI which would be expressed as a positive value: the same method has been used in previous studies involving both PPI and PPF measurements in schizophrenia (e.g. Hazlett et al., 1998).

The relationship of PPI (averaged over 30-, 60-, 90-, 120- and 150-ms prepulse-to-pulse interval trials) and PPF with the age of onset, positive symptoms, negative symptoms, general psychopathology, duration of illness, and the number of previous psychotic episodes in the patient group (across the entire sample and also separately for men and women) and current age (separately for patients and controls) was evaluated using Spearman's rank order correlations.

The effects of diagnosis and sex on latencies to response peak were examined by 2 (Group) \times 2 (Sex) \times 7 (Trial Type: pulse-alone and different prepulse trials) \times 4 (Block) MANOVA, followed by a MANCOVA with age entered as a covariate.

All analyses were performed using SPSS (Version 10). The α level for significance (two-tailed) was set at $p < 0.05$, unless specified otherwise.

3. Results

3.1. Amplitude and habituation

There was significant habituation of the startle response with repeated presentation of pulse-alone trials as indicated by a significant main effect of Block ($F = 3.94$, $df = 3,70$, $p = 0.01$; linear $F = 10.29$, $df = 1,72$, $p = 0.002$). The rate of habituation did not vary as a function of diagnosis or sex as there was no interaction between Block and any other factor. However, the amplitude over the entire session was influenced by a significant Group \times Sex interaction ($F = 6.29$, $df = 1,72$, $p = 0.01$). Men with schizophrenia did not differ from healthy men ($F < 1$) but women with schizophrenia had higher response amplitude than healthy women ($F = 6.58$, $df = 1,32$, $p < 0.02$). Women with schizophrenia also had higher response amplitude than men with schizophrenia ($F = 6.79$, $df = 1,39$, $p = 0.01$) but there was no difference between healthy men and healthy women ($F < 2$). Correlational analysis revealed a significantly negative relationship ($\rho = 0.33$, $df = 42$, $p = 0.03$) between response amplitude and the dose of antipsychotic medication across the entire sample. Covarying for the dose of medication, however, did not abolish the significant effect of Sex in response amplitude in schizophrenia patients, though it somewhat reduced the power of this effect ($F = 4.41$, $df = 1,38$, $p = 0.04$). Mean response amplitudes over the four blocks for schizophrenia patients and healthy controls, classified by sex, are presented in Table 2.

3.2. PPI

The overall four-way (Group \times Sex \times Trial Type \times Block) MANOVA revealed a significant

Table 2

Mean (standard errors of mean, S.E.M.) response amplitudes over the four blocks of four pulse-alone trials in patients with schizophrenia and healthy controls

	Patients		Controls	
	Women Mean (S.E.M.)	Men Mean (S.E.M.)	Women Mean (S.E.M.)	Men Mean (S.E.M.)
Block 1	727.69 (143.31)	420.64 (75.84)	413.72 (88.88)	497.13 (138.88)
Block 2	561.98 (127.59)	298.22 (42.78)	344.73 (59.16)	430.36 (151.17)
Block 3	484.13 (135.09)	268.41 (33.21)	266.18 (53.79)	388.83 (128.52)
Block 4	483.07 (118.22)	303.012 (55.27)	273.97 (66.07)	398.47 (118.60)

main effect of Group ($F = 4.79$, $df = 1,73$, $p = 0.03$) indicating less PPI in patients relative to controls. However, it also revealed a significant Group \times Sex interaction ($F = 11.69$, $df = 1,73$, $p = 0.001$; see next paragraph for specific effects in this interaction). Other significant effects included a main effect of Trial Type ($F = 14.94$, $df = 4,70$, $p < 0.001$) with significant linear ($F = 35.84$, $df = 1,73$, $p < 0.001$) and quadratic ($F = 21.55$, $df = 1,73$, $p < 0.001$) trends (see Fig. 1 for PPI with different trial types across the entire session in the patient and control groups, classified by sex) and a Trial type \times Block effect ($F = 3.19$, $df = 12,62$, $p = 0.001$) indicating a reduction in PPI from Block 1 to Block 4 for all trial types except for 30-ms prepulse trials [linear F (Trial type \times Block) = 8.65, $df = 1,73$, $p = 0.004$] (see Appendix B for a full set of results).

The Group \times Sex effect in PPI, noted earlier, remained significant ($F = 12.88$, $df = 1,71$, $p = 0.001$) after covarying for current age and response amplitude over the pulse-alone trials. Subsequent analysis (MANCOVA with age and response amplitude as covariates) demonstrated that the effect of Group (patients versus controls) was significantly present for men ($F = 4.17$, $df = 1,38$, $p = 0.05$) showing less PPI in men with schizophrenia compared to healthy men, but not in women with schizophrenia compared to healthy women ($F < 1$). Sex effect in PPI was significantly present in controls ($F = 9.15$, $df = 1,31$, $p = 0.005$) revealing, as expected, less PPI in women compared to men. Sex effect was also present in the patient group ($F = 4.34$, $df = 1,38$, $p = 0.04$) but with

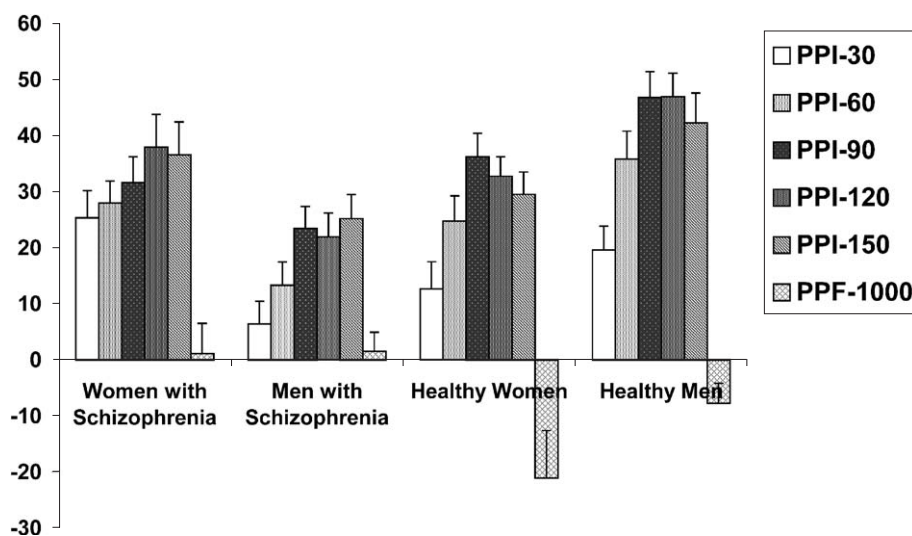


Fig. 1. Mean percentage response modulation (error bars show +1 S.E.M.) over the entire session with different prepulse-to-pulse interval trials (producing PPI or PPF) for patients with schizophrenia and healthy comparison subjects. Negative values represent response facilitation with 1000-ms prepulse-to-pulse interval trials.

an opposite pattern to that seen in controls, i.e. more PPI in affected women compared to affected men (see Fig. 1).

Further analysis to examine PPI in male and female patients after co-varying for age of illness onset, positive symptoms, negative symptoms, general psychopathology, and the number of previous psychotic episodes, age and pulse-alone amplitude (n reduced to 24 male patients and 14 female patients; see Section 2.1) showed a reduced effect of Sex ($F=2.44$, $df=1,30$, $p=0.13$), but revealed a significant Sex \times Trial Type interaction ($F=3.11$, $df=4,27$, $p=0.03$). Probing further into this interaction revealed that affected women still had significantly more PPI than affected men with 30-ms prepulse trials ($F=6.06$, $df=1,30$, $p=0.02$) but did not differ significantly for PPI with any other trials ($F_s < 2$). The effects of smoking status in male or female patients, of anticholinergic use in male patients, and of menopausal status (menstruating versus post-menopausal women) in PPI or PPF were not significant ($F_s < 2$).

Across the entire patient sample, age, age at the onset of illness, positive symptoms, negative symptoms, general psychopathology, number of previous episodes, the duration of illness and medication dose did not significantly relate to PPI. However, when

examined separately for male and female patients, the age of illness onset correlated positively (i.e. earlier onset associated with less PPI; $\rho=0.39$, $df=26$, $p=0.05$) and age correlated negatively ($\rho=-0.50$, $df=26$, $p=0.005$) with PPI in male patients. No other correlations were significant in male or female patients. Current age did not correlate with PPI in controls.

3.3. PPF

The overall three-way (Group \times Sex \times Block) MANOVA revealed only a main effect of Group ($F=3.89$, $df=1,73$, $p=0.05$) suggesting that patients with schizophrenia, as a group, showed reduced PPF, as compared to the group of healthy controls. No other effects were significant (Appendix B). The effect of Group, however, was abolished ($F=0.02$, $df=1,71$, $p=0.90$) when the pulse-alone amplitude and age were co-varied for, with age showing a strong effect of its own ($F=8.60$, $df=1,71$, $p=0.005$). Current age did not correlate with PPF (averaged over four blocks) when examined separately in controls ($\rho=0.13$, $df=35$) or patients ($\rho=0.07$, $df=42$) but it was positively correlated ($\rho=0.31$, $df=77$, $p=0.006$; increasing age predicting less PPF, since greater nega-

Table 3

Mean (standard error of mean, S.E.M.) latencies to response peak (in ms) for pulse-alone trials and different prepulse-to-pulse (PrP) interval trials over the entire session

	Patients		Controls	
	Women Mean (S.E.M.)	Men Mean (S.E.M.)	Women Mean (S.E.M.)	Men Mean (S.E.M.)
<i>Trial type</i>				
Pulse-alone	75.28 (2.82)	73.27 (3.30)	65.80 (1.76)	64.03 (2.55)
PrP-30	71.09 (3.30)	70.14 (3.39)	57.93 (2.05)	56.44 (3.07)
PrP-60	70.89 (3.63)	72.11 (2.81)	60.17 (2.22)	58.54 (2.47)
PrP-90	69.82 (3.45)	70.56 (2.43)	60.98 (2.73)	59.23 (2.91)
PrP-120	75.00 (3.86)	71.94 (2.83)	62.26 (2.80)	60.01 (2.55)
PrP-150	60.40 (3.01)	57.06 (3.42)	67.50 (2.63)	71.22 (3.44)
PrP-1000	69.73 (2.64)	68.76 (2.24)	61.20 (2.55)	60.69 (2.12)

tive values mean more PPF) with PPF across the combined (patients and controls) sample. PPF did not significantly correlate to any clinical variables in patients.

3.4. Latencies to response peak

There was no effect of Sex and no Group \times Sex interaction ($F_s < 1$). A significant effect of Trial Type was present ($F = 10.52$, $df = 6,68$, $p < 0.001$) indicating reliably shorter latencies with 30- and 1000-ms prepulse-to-pulse interval trials, compared to latencies over the pulse-alone trials (Table 3). There were no main or interactive effects involving the Block factor. There was a main effect of Group showing longer latencies in patients (Group: $F = 19.38$, $df = 1,73$, $p = 0.05$; see Table 3) but it became non-significant when current age was entered as a covariate ($F = 2.83$, $df = 1,72$, $p = 0.10$; see Table 3).

4. Discussion

Confirming our hypotheses, (i) PPI was reduced in patients with schizophrenia, as a group, compared to healthy subjects, (ii) PPI was reduced in men with

schizophrenia, especially in association with an earlier onset of illness, relative to healthy men, and (iii) healthy women had less PPI compared to healthy men, and (iv) there was no deficit in PPI in women with schizophrenia compared to healthy women. The study also observed a lack of significant sex effect in PPF (if anything, healthy women showed non-significantly more PPF than healthy men), and although there was a marginally significant difference in PPF between patients and controls, it appeared to be associated with age rather than the schizophrenia disease process.

Our finding of reduced PPI in the patient group compared to the control group (regardless of sex) replicates previous reports using the same paradigm in male samples (Kumari et al., 1999, 2000, 2002; Parwani et al., 2000; Duncan et al., 2003) or mixed samples of both sexes (Braff et al., 1978, 1992, 2001a; Dawson et al., 1993; Bolino et al., 1994; Hazlett et al., 1998; Cadenhead et al., 2000; Weike et al., 2000; Leumann et al., 2002; Ludewig and Vollenweider, 2002; Oranje et al., 2002; Perry et al., 2002; Mackeprang et al., 2002; all but one of these studies have included more affected men than affected women; see Appendix A2). However, this group difference was mainly due to reduced PPI in men with schizophrenia compared to healthy men: there was no difference in PPI between affected women and same sex controls.

The simplest explanation for our observation of no deficit in PPI in women with schizophrenia (compared to healthy women) is that healthy women themselves showed relatively low levels of PPI, a common observation in studies involving healthy men and women (Swerdlow et al., 1993, 1997, 1999; Abel et al., 1998; Kumari et al., 2003). However, it can still be speculated, given that we found significantly higher PPI in affected women than affected men (which was in part explained by clinical variables) that good responsiveness to anti-dopaminergic medication leads to some improvement in PPI (or greater improvement than seen in affected men) over a longer term in women with chronic schizophrenia. We had examined the possibility, given the evidence for the influence of reproductive hormones contributing to sex differences in human PPI (Swerdlow et al., 1997), of whether mainly post-menopausal women contributed to higher PPI in the

group of affected women, compared to affected men, but this was not supported by the data (see Results). Given previous observations of positive effects of nicotine/cigarette smoking in PPI (Duncan et al., 2001; Kumari et al., 2001a), especially in relation to sex (Della Casa et al., 1998), we also examined the possibility of a difference in the smoking status of women and men with schizophrenia perhaps accounting for a difference in PPI between these two groups. Our data, however, failed to support this possibility (especially, there was no difference in PPI in smoking and non-smoking female patients). Similarly, the use of anticholinergic medication did not explain PPI deficits in men with schizophrenia. The only variables to relate to PPI in male patients were the age of illness onset (earlier onset being associated with lower PPI) and age. The observation concerning the age of onset and PPI association was only marginally significant and did not withstand correction for multiple correlations. We, however, believe it to represent a true effect as it replicated our earlier observations of age of onset effect in PPI in (a different sample of) chronic male schizophrenia patients (Kumari et al., 2000). It is also worth noting that we have failed to observe any effect of age of onset in PPI in a sample of first episode male schizophrenia patients (Kumari et al., 2001b), so we believe that the observed age of onset effect in PPI in chronic male patients (current results; Kumari et al., 2000) represents some improvement in PPI over the course of illness in later onset male schizophrenia patients (or more improvement than in patients with an earlier onset), perhaps in relation to their responsiveness to antipsychotic medication (Meltzer et al., 1997). It is possible that sex differences in normal brain maturation rate and also in schizophrenia related brain deficits (Cowell et al., 1996; Bryant et al., 1999) in interaction with response to medication (Smith et al., 1998) and/or reproductive hormones (Seeman and Lang, 1990) led to the observation of a significant relationship between the (earlier) onset of illness and PPI in affected men, but not in affected women. However, given the inconsistency in the literature regarding sex differences in schizophrenia (Hafner, 2003), this remains to be the subject for further investigation.

A recent observation (Rahman et al., 2003; also observed by Neal Swerdlow, personal communica-

tion), with some relevance to current results, is that healthy homosexual women show more PPI compared to PPI in heterosexual healthy women (all women tested during first 10 days of the menstrual cycle) and similar to that observed in heterosexual men. This raises the question whether there is greater prevalence of homosexuality in female schizophrenia patients than the general population. Unfortunately, we did not collect data on sexual orientation for the patient group (the data collection for the current study was nearly over when we became aware of the influence of sexual orientation in PPI). It should, however, be noted that although women with schizophrenia had higher PPI than men with schizophrenia, they did not have *significantly* more PPI than healthy women.

This study did not find a significant sex difference in PPF, but found a marginally significant difference in PPF between patients and controls (regardless of sex), that seemed to be related to the effects of age rather than the illness. Although one recent study (Ludewig and Vollenweider, 2002) has reported PPF deficits in patients with deficit syndrome, but not in those with non-deficit syndrome, with very similar stimulus parameters to that used in the present study, another study (Leumann et al., 2002) from the same laboratory did not observe PPF deficits in schizophrenia patients. It is possible that the effects seen in Ludewig and Vollenweider (2002) were confounded by the effects of age, as seen in the current study, where patients with deficit syndrome were considerably older (mean age = 42 years; range = 26–62) than those with non-deficit syndrome (mean age = 33 years; range = 26–49). There have also been other studies (Braff et al., 1978; Bolino et al., 1994) that did not find PPF deficits in schizophrenia. Although it is possible that the use of a discrete prepulse stimulus has more power to detect PPF deficit as noted for PPI by Braff et al. (2001a), given the inconsistency in existing literature and the observation that PPF difference between patients and controls in this study seems to be associated with age rather than illness, it remains to be established whether or not (passive) PPF is compromised as a function of the schizophrenia disease process. The current study was rather limited for the examination of sex/disease effects in PPF deficits, since it only used one prepulse-to-pulse interval to elicit PPF. Furthermore,

although it included 15 or more subjects in each cell (Group \times Sex) to gain stability for the data, the current sample was somewhat asymmetrical in the sex breakdown by subject group sizes: this, although typical of most studies involving schizophrenia patients (see Appendix A2), makes the study less than ideal for an investigation of sex differences. Future studies should examine PPF differences between patients and controls with the use of a wider range of prepulse-to-pulse intervals to elicit PPF and a more balanced sample with regard to distribution of sexes within the groups.

The finding of higher response amplitude, controlling for age, in women with schizophrenia compared to other groups, has also emerged for the first time. The dose of antipsychotic medication was inversely related to response amplitude in patients across the entire sample, and women, on average, were receiving lower doses (Table 1). Covarying for the dose of medication, however, did not abolish (but did reduce) the difference in response amplitude between men and women with schizophrenia. Furthermore, the amplitude of the response in men with schizophrenia, although somewhat lower, was not significantly lower compared to healthy men. Further studies could thus examine whether higher response amplitude in women with schizophrenia seen in this study was also associated with some other specific effects (for example anxiety) which are known to be associated with elevated startle responding (Kumari et al., 2001c; Grillon, 2002). Differences in PPI, however, were not abolished after co-varying for pulse-alone amplitude, so the effects described and discussed earlier in relation to PPI still remain valid. Future research could (a) use paradigms with wider range of prepulse-to-pulse intervals in order to fully investigate these observed sex differences in startle modification deficits in

schizophrenia, (b) investigate whether the sex differences on the PPI are in some way related to brain structural and functional differences or neurochemical difference between the sexes, (c) examine whether the same sex differences, as seen in this study of medicated patients, emerge in patients within the first psychotic episode and those with schizotypal personality disorder, who also show reduced PPI (Cadenhead et al., 2000).

To conclude, this study replicated previous observations of reduced PPI in patients with chronic schizophrenia compared to healthy controls, but further found that this difference was mainly due to the severe loss of PPI in men with schizophrenia in association with an earlier age of illness onset. Also replicating several previous reports, healthy women were found to have less PPI than healthy men. Women with schizophrenia showed more PPI than men with schizophrenia: this difference was, to some degree, explained by clinical variables. Significant sex differences were not found for PPF in healthy controls, and reduced PPF in patients (regardless of sex) relative to controls seemed to be related to age, rather than the illness. Given the pattern of effects observed in this study, we suggest that future studies should routinely examine the effects of age and sex in investigation of PPI deficits, their neural correlates and possible normalization by relevant pharmacological means in patients with schizophrenia and related populations.

Acknowledgements

Veena Kumari holds a Wellcome Trust Senior Research Fellowship in Basic Biomedical Science. We are grateful to Ms. Sinead McCabe for her help with manuscript preparation.

Appendix A

A.1. Studies (in chronological order) of sex effects in PPI and PPF of healthy subjects

Reference	Gender distribution	PPI (SOA in ms)	PPF (SOA in ms)	Prepulse characteristics	Pulse characteristics	Background	Menstrual phase	Sex effects
Blumenthal and Gescheider (1987)	13 Females, 13 Males	Yes (50, 100, 200, 300)	No	20 ms sinusoidal, 55-Hz pulse 20 dB above subject's probability threshold	50-ms 85 dB WN	40 dB WN	Unspecified	Less PPI in females (indicated by lower response probability in men)
Ornitz et al. (1991)	45 Females ^a , 50 Males ^b	Yes (120, 250)	Yes (800, 2000)	4 ms 75 dB 1000-Hz T for PPI, Continuous 75 dB 1000-Hz T for PPF	50 ms 104 dB WN	Unspecified	Between day 5 and 12 of the menstrual cycle ^a	Less PPI in females No sex effect in PPF ^c
Swerdlow et al. (1993)	18 Males, 19 Females	Yes (30, 60, 120)	No	Discrete 20 ms 72, 74, 78 and 86 dB WN	40 ms 118 dB WN	70 db WN	Unspecified	Less PPI in females
Swerdlow et al. (1995)	18 Males, 12 Females	Yes (60)	No	Discrete 20 ms 72, 74, 78 and 86 dB WN	40 ms 118 dB WN	70 db WN	Unspecified	Less PPI in females
Swerdlow et al. (1997)	10 Males, 42 Females	Yes (60)	No	Discrete 20 ms 72, 74, 78 and 86 dB WN	40 ms 118 dB WN	70 db WN	Females tested on different days of the cycle	Less PPI in females PPI higher in women tested on days 1-7 than those tested on days <15 after the last menstrual period
Abel et al. (1998)	8 Males, 7 Females	Yes	No	Discrete 20 ms 85 dB WN	40 ms 116 dB WN	70 dB WN	Days 2-4 of self-reported menstrual cycle	Less PPI in females
Swerdlow et al. (1999) ^d	360 Males, 419 Females	Yes ^d	No	Unspecified ^d	Unspecified ^d	Unspecified ^d	Unspecified ^d	Less PPI in females
Ludewig et al. (2003b)	27 Males, 28 Females ^c	Yes (30, 60, 120, 240)	Yes (2000)	Discrete 20 ms 86 dB WN	40 ms 115 dB WN	70 dB WN	Early follicular phase ^c	No sex effect (PPI and PPF not examined separately)
Kumari et al. (2003)	15 Males, 15 Females	Yes (120)	No	Discrete 20 ms 85 dB WN	40 ms 115 dB WN	70 dB WN	Days 1-7 of self-reported menstrual cycle	Less PPI in females

SOA=Stimulus-onset-asynchrony; M=Male, F=Female; T=Tone, WN=White noise.

^aThirty-three of 45 female subjects were children (ten 4 years old, ten 5 years old and thirteen 8 years old). ^bData taken from Ornitz et al. (1986) for comparison with female subjects and included 36 children (ten 4 years old, ten 5 years old and sixteen 8 years old). ^cGender differences not seen for those aged 4 or 5 years. ^dRetrospective analysis of data from normal subjects included in previously published reports from the authors' group. ^eThirteen of 28 subjects >40 years old (seven between 40 and 49 years; six between 50 and 60 years) but no information provided on menopausal status.

A.2. PPI and PPF studies (in chronological order) which included schizophrenia patients of both sexes

Reference	Group and Sex distribution	PPI examined (SOA in ms)	PPF Examined (SOA in ms)	Prepulse characteristics	Pulse characteristics	Background	Deficits Patients < Controls (SOA/subsample)	Symptom correlates	Sex effects
Braff et al. (1978)	Patients: 5 M, 7 F, Controls: 11 M, 9 F	Yes (30, 60, 120, 240, 500)	Yes (2000)	Continuous 71 dB 1000-Hz T	50 ms 104 dB WN	Unspecified	Yes (60 ms)	NE	NE
Grillon et al. (1992)	Patients: 12 M, 2 F, Controls: 12 M, 2 F	Yes (120)	No	Discrete 20 ms, 75, 80, 85 and 90 dB WN	40 ms 106 dB WN	70 db WN	Yes	NE	NE
Braff et al. (1992)	27 Patients: Sex ^a , 26 Controls: Unspecified ^a	Yes (30, 60, 120)	No	Discrete 20 ms 85 dB WN	40 ms 116 dB WN, 40 ms 30-psi air puffs	70 dB WN	Yes	NE	NE
Dawson et al. (1993)	Patients: 13 M, 2 F, Controls: 12 M, 2 F	Yes (60, 120, 240)	Yes (2000)	25 ms 70 dB 800-Hz T (attend), 1200-Hz T(ignore)	50 ms 100 dB WN	Unspecified	Yes (During attend to the prepulse condition only)	NE	NE
Bolino et al. (1994)	Patients: 10 M, 8 F, Controls: 13 M, 7 F	Yes (30, 60, 120, 750)	Yes (2000)	1 ms 0.92 mA electrocutaneous stimulus	1 ms 3.7 mA or greater electrostimulus	Unspecified	Yes (120)	NE	NE
Hazlett et al. (1998)	Patients: 11 M, 5 F, Controls: 9 M, 6 F	Yes (120, 240)	Yes (4500)	25 ms 70 dB 800-Hz (attend), 1200-Hz (ignore), 500-Hz (novel) T	40 ms 104 dB WN	45 dB WN	Yes (During attend to the prepulse condition only)	NE	NE
Cadenhead et al. (2000)	Patients: 16 M, 7 F, Controls: 7 M, 18 F	Yes (30, 120)	No	Discrete 20 ms 86 dB WN	40 ms 115 dB WN	70 dB WN	Yes (30 ms)	NE	NE (covaried for sex)
Weike et al. (2000)	Patients: 17 M, 10 F, Controls: 8 M, 6 F	Yes (30, 60, 120, 240)	No	Discrete 20 ms 85 dB 1000-Hz T	40 ms 105 dB	Unspecified	Yes (Reduced PPI in 5 unmedicated patients; non-significantly less PPI in medicated patients)	Negatively correlated with negative symptoms	
Braff et al. (2001a,b)	Patients: 16 M, 9 F, Controls: 15 M, 15 F	Yes (60)	No	Discrete 20 ms 85 dB WN or 1000 Hz T and continuous 85 dB WN or 1000-Hz T	40 ms 115 dB WN	70 dB WN	Yes	NE	NE

Appendix A.2 (continued)

Reference	Group and sex distribution	PPI examined (SOA in ms)	PPF Examined (SOA in ms)	Prepulse characteristics	Pulse characteristics	Background	Deficits Patients < Controls (SOA/ subsample)	Symptom correlates	Sex effects
Ludewig and Vollenweider (2002)	Patients: 49 M, 18 F, Controls: 27 M, 17 F	Yes (30, 60, 120, 240)	Yes (2000)	Discrete 20 ms 86 dB WM	40 ms 115 dB WN	70 dB WN	Yes (60, 240 and 2000 ms SOAs)	Reduced 60 ms SOA PPI and reduced PPF in deficit syndrome. Reduced 240 SOA PPI in non-deficit syndrome. 60 ms PPI negatively correlated with negative symptoms	NE
Leumann et al. (2002)	Patients: 25 M, 8 F, Controls: 13 M, 6 F	Yes (30, 60, 120, 240)	Yes (2000)	Discrete 20 ms 86 dB WM	40 ms 115 dB WN	70 dB WN	Yes (Reduced PPI with 60 ms SOA in 13 M and 4 F patients on typical antipsychotics; No deficit in remaining patients, all on atypical antipsychotics)	NE	NE
Oranje et al. (2002)	Patients: 31 M, 13 F, Controls: 24 M, 11 F	Yes (120)	No	Discrete 30 ms 85 dB 1500 Hz T	30 ms 115 dB, 1500 Hz T	Unspecified	Yes (Reduced PPI in 16 M and 11 F patients on typical antipsychotics; No deficit in remaining patients, all on atypical antipsychotics)	NE	NE
Perry et al. (2002)	Patients: 25 M, 16 F, 13 Controls: Sex Unspecified	Yes (30, 60, 120)	No	Discrete 20 ms 95 dB WN	40 ms 115 dB WN	70 dB WN	Yes (60 and 120 SOA only)	No relationship with symptoms	NE
Mackeprang et al. (2002)	Patients: 14 M, 6 F, Controls: 15 M, 5 F	Yes (30, 60, 120)	No	Discrete 20 ms 85 dB WN	40 ms 116 dB WN	70 dB WN	Yes	No relationship with symptoms	NE

SOA = Stimulus-onset-asynchrony; M = Male, F = Female; T = Tone, WN = White noise; NE = Not examined.

^aStudy initially included 39 patients (24 M, 15 F) and 37 controls (15 M, 22 F) but gender distribution not specified for the final sample after excluding 12 patients and 11 controls who were startle non-responders.

Appendix B. Results of MANOVAs/ANOVAs for PPI and PPF

Factor	PPI			PPF		
	F	df	p	F	df	p
<i>Patients versus controls (entire sample)</i>						
Group	4.79	1,73	0.03	3.89	1,73	0.05
Sex	0.21	1,73	n.s.	1.86	1,73	n.s.
Group × Sex	11.69	1,73	<0.001	0.03	1,73	n.s.
Trial type	14.95	4,70	<0.001			
Trial type × Group	2.03	4,70	n.s.			
Trial type × Sex	0.84	4,70	n.s.			
Trial type × Group × Sex	1.78	4,70	n.s.			
Block	2.54	3,71	n.s.	1.48	3,71	n.s.
Block × Group	2.38	3,71	n.s.	0.72	3,71	n.s.
Block × Sex	1.91	3,71	n.s.	1.82	3,71	n.s.
Block × Group × Sex	0.48	3,71	n.s.	0.44	3,71	n.s.
Trail type × Block	3.19	12,62	0.001			
Trial type × Block × Group	0.95	12,62	n.s.			
Trial type × Block × Sex	0.56	12,62	n.s.			
Trial type × Block × Group × Sex	1.20	12,62	n.s.			
<i>Men with schizophrenia versus healthy men</i>						
Group	14.87	1,40	<0.001			
Trial type	10.11	4,37	<0.001			
Trial type × Group	0.88	4,37	n.s.			
Block	0.14	3,38	n.s.			
Block × Group	0.58	3,38	n.s.			
Trial type × Block	2.69	12,29	0.02			
Trial type × Block × Group	0.92	12,29	n.s.			
<i>Women with schizophrenia versus healthy women</i>						
Group	0.84	1,33	n.s.			
Trial type	5.53	4,30	0.002			

Appendix B (continued)

Factor	PPI			PPF		
	F	df	p	F	df	p
<i>Women with schizophrenia versus healthy women</i>						
Trial type × Group	1.00	4,30	n.s.			
Block	3.27	3,31	0.03			
Block × Group	2.05	3,31	n.s.			
Trial type × Block	0.89	12,22	n.s.			
Trial type × Block × Group	1.04	12,22	n.s.			
<i>Healthy men versus healthy women</i>						
Sex	9.14	1,33	0.005			
Trial type	11.88	4,30	<0.001			
Trial type × Sex	0.29	4,30	n.s.			
Block	1.86	3,31	n.s.			
Block × Sex	1.54	3,31	n.s.			
Block × Trial type	2.13	12,22	n.s.			
Block × Trial type × Sex	0.58	12,22	n.s.			
<i>Men with schizophrenia versus women with schizophrenia</i>						
Sex	3.92	1,40	0.05			
Trial type	4.45	4,37	0.005			
Trial type × Sex	2.63	4,37	0.05			
Block	2.61	3,38	n.s.			
Block × Sex	0.54	3,38	n.s.			
Block × Trial type	1.31	12,29	n.s.			
Block × Trial type × Sex	1.17	12,29	n.s.			

n.s. = not significant.

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