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ORIGINAL PAPER

No association between prepulse inhibition of the startle reflex and neuropsychological deficit in chronic schizophrenia

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Abstract Sensorimotor gating deficits are relevant in schizophrenia and can be measured using prepulse inhibition (PPI) of the startle reflex. It is conceivable that such deficits may hinder the cognitive functions in schizophrenia patients. In this study, using PPI and a neuropsychological battery, we studied this possibility in a group of 23 acute, neuroleptic-free schizophrenia patients and 16 controls. A non-significant decrease in PPI was found in the patients as compared to the controls, as well as significant differences in the performance of Trail A and B in Wisconsin Card Sorting and Digit/Symbol Tests. No statistically significant correlations between PPI and neuropsychological performance were found after the correction for multiple comparisons in any group. Our results suggest that PPI deficits in schizophrenia patients may not contribute to the cognitive deficits typical of that illness, at least in patients with a non-significant PPI decrease.

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Introduction

Sensorimotor gating can be studied with procedures assessing prepulse inhibition (PPI) of the startle reflex [9]. In recent decades, many studies have shown impaired PPI values in schizophrenia patients [4, 9, 10]. These PPI deficits may be especially relevant to the cognitive deficits found in schizophrenia, since they may contribute to overloading the cortical processing of incoming stimuli. PPI deficits may represent a neurobiological phenotype in at least some cases of schizophrenia [29].

Previous results on the association between PPI and cognition have yielded conflicting results. In general, studies on healthy subjects support such an association [2, 3, 11], but this is less clear in schizophrenia. Some reports have shown no association between sensorimotor gating and cognition [7, 37], while other data suggest a relation between PPI deficit and different neurocognition measures in that illness [13, 22, 42].

Since cognition assessments were different across those studies, it seems conceivable that those discrepancies might relate in part to an association between gating deficits and some, but not all of the neuropsychological deficits in schizophrenia. Recently, the measurement and treatment research to improve cognition in schizophrenia (MATRICS) consensus has proposed six cognitive dimensions for those deficits in schizophrenia [32]. These dimensions represent an opportunity to refine the study of the brain deficits underlying cognitive deficits in schizophrenia.

In this study, to further investigate the involvement of gating deficits of cognition in schizophrenia, we used PPI

and a neuropsychological battery based on the MATRICS consensus to assess a sample of acute schizophrenia patients and healthy controls. Our hypothesis was that an association would have been found between cognitive and PPI deficits.

Patients and methods

Subjects

Our sample initially included 25 patients (11 males) diagnosed with paranoid schizophrenia. All of them were neuroleptic-free at the time of inclusion, since they had quit their medication for a period of more than 1 month and, as a result of a psychotic crisis, had to be admitted to the psychiatric unit of our hospital. PPI and neuropsychological data were available in 23 of the 25 cases (10 out of 11 males; one case was excluded because an MRI unveiled a brain tumor and also another, whose PPI records were not useful). None of these patients could be considered as treatment resistant according to the usual criterion of a prior lack of response to two or more antipsychotics. None of them had been treated with clozapine previously.

Patient diagnosis was confirmed using the structured clinical interview for diagnostic and statistical manual (SCID, patients' version) and data obtained from clinical interviews, together with information from the patients' families and the clinical staff. All patients were in a short-term psychiatric unit. The Positive and Negative Syndrome Scale [20] was used to evaluate their symptoms (Table 1). After informed consent, patients and controls underwent PPI and a neuropsychological battery (see below).

Sixteen healthy controls (nine males) with no personal or familial psychiatric background were also included. To match them with the patient group, it was ensured that none of the subjects had a college-level education, and efforts were also made to match the parental school years. According to the Hollingshead and Frederick scale [17], no differences in age or parental socioeconomic level were observed between the patient and control groups (Table 1). There were no significant differences in parental educational level between patients and controls.

Table 1 Clinical and demographic characteristics in patients and controls shown as mean (standard error)

	Patients ($n = 23$)	Controls ($n = 16$)	t(p)
Age (years)	37.5 (2.1)	29.4 (2.4)	2.8 (0.005)
Education (years)	10.7 (1.3)	13.7 (0.8)	−1.51 (0.13)
Parental SES	1.8 (0.2)	2.3 (0.3)	−1.73 (0.10)
Duration (years)	10.1 (8.2)	NA	NA
PANSS-P	27.7 (1.3)	NA	NA
PANSS-N	23.9 (1.4)	NA	NA
PANNS-T	93.1 (3.4)	NA	NA

Comparisons between patients and controls were performed using Student's *t* test

SES socioeconomic status, *PANSS* positive and negative symptoms scale

Sixteen patients and six controls were smokers. Neither patients nor controls smoked for at least 2 h prior to PPI testing. Prior to the PPI assessment, nicotine supplementation was given to smoker patients from the time of admission, except for 2 h preceding this assessment. Smoker controls were not instructed to restrict their tobacco consumption except for the 2 h abstinence prior to PPI assessment. This was done to avoid the acute effects of nicotine on PPI and to homogenize the data acquisition conditions in the patients and controls by avoiding the possible long-lasting effects of nicotine withdrawal and its disturbing effects on the smokers. Patients also received nicotine replacement at the time of cognitive testing without prior interruption. Controls who smoked were not required to stop smoking prior to cognitive testing.

Exclusion criteria were: any other axis I diagnosis, any neurological illness, a history of cranial trauma with loss of consciousness, past substance dependence, excluding nicotine or caffeine, drug abuse during the last 3 months (current consumption being ruled out by urinalysis), and any current treatment with known effects on the central nervous system. None of the patients or controls had received mood stabilizers, antidepressants, or depot neuroleptics over the 6 months preceding the study. All patients and controls underwent a cautionary MRI scan to exclude any abnormality of neurological relevance, as judged by an expert radiologist.

After the subjects had been given detailed information about the study, written informed consent was obtained from each of them and from a first-degree relative. The research and ethics boards of the participating institutions endorsed the study.

PPI acquisition and processing

The acoustic startle test session for measuring the PPI consisted of several parts, with a total time of acquisition of about 30 min, after the subjects' hearing acuity had been tested. During the session, the subjects were sitting comfortably in a double-walled, sound-attenuated, slightly dark chamber. Ambient room noise was measured using an artificial ear coupled to the headphones.

First, the recording electrodes were connected while the subjects were comfortably sitting in a reclined chair (10–15 min). They were asked to remain relaxed, with their

eyes open. Then, with the chamber closed, a 5 min acclimatizing period began, with a background noise of 60 dB, which was maintained for the rest of the session. Acoustic stimuli were delivered to the subjects binaurally through headphones (DR-531B-14; Nihon Kohden America, Inc., USA).

The test consisted of five blocks of two different trials: pulse alone (105 dB, 50 ms bursts of white noise) and acoustic startle stimuli preceded by a 50 ms prestimulus (prepulse: 75 dB, 20 ms bursts of white noise), delivered binaurally through headphones. The session began and ended with a block of three startling stimuli (pulse alone). Between these two blocks, there were three blocks of three prepulse–pulse and one pulse-alone trial, presented in a pseudo-random order. The mean intertrial intervals were 15 s and the interblock intervals were 120–140 s. The entire session lasted approximately 13 min.

EMG recordings of the orbicularis and masseter muscles were obtained with a Neuropack Kohden electromyograph (Nihon Kohden). The bin width for the electromyographic response was 300 ms, including 50 ms of basal activity and 100 ms following the response, and was bandpass filtered (1–1,000 Hz).

PPI was defined according to the formula:

$$\%\text{PPI} = 100*[(\text{magnitude of pulse alone} - \text{magnitude of prepulse - pulse})/\text{magnitude of pulse alone}]$$

To reduce the number of comparisons and given the small number of patients, we selected only the percentage of attenuation of the amplitude of the startle reflex (ASR) response (% PPI) in the orbicularis muscle as the variable to be assessed as an index of sensorimotor gating processes. Other data obtained in the study, such as the acoustic startle response (amplitude and latency), are not directly related to pre-attentional or attentional processes and hence were not analyzed in depth.

Neuropsychological assessment

Neuropsychological assessment was carried out in the first week of the study, after the patients had received between 5 and 7 days of treatment, so that the bias related to the acute psychotic state could be minimized. All cases had been treated with quetiapine (400 mg) during that period. The investigators (CM and JP) were blind to the psychopathological assessments of the patients. The battery was composed of: Trail-Making Test A and B (TMT A and B), the WAIS Digit–Symbol Subtest, the FAS Fluency Test, the Stroop Test and the Wisconsin Card Sorting Test (WCST). This battery was designed to asses the separable cognitive domains of speed processing, attention/vigilance, working memory, visual learning and memory, and problem-solving. These domains have been identified on the basis of reviews of literature and expert consensus, and may have different substrates [32]. Moreover, a Spanish adaptation of the National Adult Reading Test was used to assess premorbid IQ (intellectual quotient) to discard mental retardation.

Description of the instruments

Trail-Making Test [1]

We included time in seconds to complete part A as a measure of processing speed, and time in seconds in part B and A as a measure of working memory.

Digit–Symbol (WAIS) [39]

This test assesses the subjects' processing speed and memory. The variable included was the final score (number of correct responses in 90 s) as a measure dependent on speed processing.

Stroop Test [36]

The interference score in this test was calculated as a measure of attention and resistance to distractibility.

Wisconsin Card Sorting Test (WCST) [15]

This test measures executive functions, in particular the subject's capacity to adopt or change cognitive strategies according to the demands of the task. We included as variables the number of completed categories and perseverative errors.

FAS fluency

We included the total words generated beginning with F, A, and S conceding 1 min for each letter.

Statistical methods

We assessed the significance of differences in sex distribution between patients and controls (χ^2 test).

Between-group (patients vs. controls) comparisons (PPI and cognition) were carried out using general linear model comparisons, with group as the independent variable and age and sex as covariates. We also planned a priori to repeat the comparisons of PPI between patients and controls separately based on sex, given the importance that this variable has on PPI.

The significance level was set at $p < 0.05$. Correlation analyses were performed using Pearson's r test, with

Bonferroni post hoc correction for multiple comparisons (set at $p < 0.01$). SPSS 15.0 was used for statistical analyses.

Results

Sex distribution was not significantly different between groups ($\chi^2 = 0.67$, $df = 1$, $p = 0.30$). Controls were significantly younger than patients (Table 1).

Prepulse inhibition

The patients showed a lower percentage of PPI with respect to controls, although this decrease did not reach statistical significance (Table 2). There were no significant effects of the covariates (age and sex) on ASR or PPI values (Table 2).

The same pattern was observed when male patients (mean 47.2 ± 37.1) and male controls (mean 49.8 ± 32.3, $z = -0.62$, $p = 0.53$) or female patients (mean 36.9 ± 39.6) and female controls (mean 56.5 ± 27.4; $z = -0.95$, $p = 0.33$) were compared.

To further explore the lack of differences in PPI related to the different proportion of smokers in both groups, we compared PPI between non-smoker patients and non-smoker controls. This comparison also revealed no significant PPI differences.

Cognitive scores

Patients scored significantly lower than controls in the Trail A and B, WCST completed categories and Digit/Symbol Tests (Table 2).

There was a significant effect of age on the number of perseverative errors in the WCST (Table 2). The other cognitive scores did not show a significant effect of sex or age.

Correlation between cognitive scores and PPI

There were no associations between the PPI measurements and cognitive scores in the patients (Table 3, $p > 0.10$ in all cases). PPI was also unrelated to the basal clinical scores (Table 3, $p > 0.10$ in all cases). In the controls, we did not detect any association between PPI and cognitive scores, except for a direct relationship between the Trail A completion time and PPI ($r = 0.60$, $p < 0.05$), which did not survive Bonferroni correction.

Discussion

In our patients, differences in PPI of the startle reflex were not significant between patients and control subjects. Such a lack of significance may have been due in part to the sample size, since our patients had PPI values similar to those found in other studies with treated schizophrenia patients [14, 25, 41]. Moreover, the magnitude of the PPI differences found between the patients and controls was similar to the baseline magnitude reported in other studies [25, 34].

Another possibility that explains the lack of any PPI decrease in our patients relates to methodological differences with respect to other studies, in terms of background noise (60 dB vs. 70 dB [34]), pulse intensity (105 dB vs. 115 dB[27]), prepulse interval and the number of baseline startle pulse-alone trials [27, 34]. However, significant PPI differences have also been reported in schizophrenia when using 60 dB background noise [21], suggesting that methodological differences may not be the only reason for the lack of a significant PPI reduction in our cases. It seems

Table 2 Baseline electrophysiological (startle reflex amplitude and its prepulse inhibition) and cognitive measurements in patients and controls (general linear model, group as factor; sex and age as covariates), shown as mean (standard error)

	Patients ($n = 23$)	Controls ($n = 16$)	Effects of group F(p)	Effects of sex F(p)	Effects of age F(p)
ASR amplitude	358.5 (135.0)	529.3 (154.9)	0.67 (0.41)	1.15 (0.30)	1.03 (0.33)
PPI (%)	46.1 (5.8)	56.9 (6.7)	0.33 (0.58)	0.27 (0.60)	1.03 (0.33)
IQ estimate	95.8 (34.2)	103.4 (21.7)	0.42 (0.53)	0.21 (0.64)	0.22 (0.63)
Trail A (s)	63.3 (11.5)	29.4 (1.8)	**5.3 (0.03)**	0.02 (0.87)	0.56 (0.47)
Trail B (s)	292.4 (54.0)	118.9 (9.1)	**4.9 (0.05)**	0.33 (0.57)	0.07 (0.78)
Stroop (interference)	2.4 (3.2)	6.5 (2.2)	3.3 (0.29)	0.49 (0.50)	0.12 (0.73)
WCST (perseverative errors, %)	16.2 (5.8)	18.1 (2.8)	3.2 (0.21)	4.20 (0.07)	**5.21 (0.04)**
WCST (categories)	2.6 (0.6)	5.0 (0.5)	**6.73 (0.02)**	0.01 (0.89)	0.24 (0.63)
Digit/symbols	24.5 (3.7)	56.5 (5.1)	**10.76 (0.001)**	0.23 (0.64)	1.36 (0.27)
FAS (words)	29.0 (1.9)	32.2 (1.8)	**0.81(0.03)**	0.17 (0.73)	0.22 (0.65)

ASR auditory startle reflex

Table 3 Correlation coefficients between PPI and cognitive measurements (Pearson's *r*)

	Trail A	Trail B	Stroop	WCST, p.e	WCST cat.	Digit/symbol	FAS	PANSS positive	PANSS negative	PANSS total
Patients	0.38	0.52	−0.23	−0.31	0.057	−0.06	−0.29	0.18	−0.33	−0.11
Controls	0.60*	0.29	0.30	−0.09	−0.41	−0.21	−0.36	NA	NA	NA

WCST p.e Wisconsin card sorting test perseverative errors (percentage), *WCST cat* Wisconsin card sorting test, categories completed

* $P < 0.05$ (uncorrected)

also possible that the likely heterogeneity within the schizophrenia patients regarding their neurobiological substrate may also contribute to the absence of such differences. Probably, as it occurs with structural [18] and functional [16] neurobiological deficits, PPI decreases are not found in all schizophrenia patients. Therefore, a proportion of our cases might not have shown PPI deficits by chance. In this line, PPI decrease may change with the clinical status in schizophrenia [30].

Nicotine may influence PPI through its acute effects or after abstinence. The acute effects of nicotine on PPI [6, 33], however, could not explain the lack of decrease in PPI of our patients, since neither the patients nor the controls smoked during the hours prior to PPI testing. However, the effects of abstinence could be expected in the PPI of the patients, since they remained in the hospital prior to PPI testing, but its confounding effect may have been minimized by the nicotine replacement therapy given to them. Non-smoker controls and patients did not show PPI differences either, although this was a small sample. Moreover, smoking abstinence would decrease PPI in schizophrenia [8], and hence abstinence in our patients would not justify the lack of a significant difference in PPI with respect to the controls. Rather, nicotine consumption in schizophrenia patients seems to increase PPI [28], which suggests that the lack of a significant PPI decrease in our patients might relate to the higher proportion of smokers in that group, masking a true PPI decrease in that group. We cannot rule out that the actual amount of nicotine consumption in both groups contributes to the lack of PPI differences.

The lack of association of PPI with neuropsychological performance in our patients is in agreement with the report of unrelated Trail-Making A and B scores and PPI measures [7]. Furthermore, there is a report of a lack of association between PPI and cognitive measures in normal subjects [37], which would agree with our data in the control group. However, significant associations between PPI measurements and perseverative errors in the Wisconsin Card Sorting Test [22] and social cognition parameters [42] have also been reported in schizophrenia, and PPI has been found to correlate with spatial processing, but not with other neurocognitive measurements [13] in that illness. In healthy controls, several groups have found a positive association between neurocognitive and PPI measurements. Bitsios et al. [3] described a relationship between increased PPI and better strategies and shorter execution times in problem-solving and working memory test in healthy males. Another study from the same group showed that such an association may depend on prefrontal dopamine transmission [12]. One group made up of medical students showed a trend-level association between PPI and interference scores in the Stroop Test [2]. Therefore, it seems that the possible relationship between gating deficits and cognitive dysfunction in healthy subjects may be weakened or even lost in schizophrenia. This speculation is supported by the association described in healthy subjects between PPI and hippocampal, parahippocampal, inferior frontal, thalamic, and superior temporal gyrus volumes [23], which are the regions consistently affected in schizophrenia [35]. Indeed, a positive association was found between prefrontal (dorsolateral and orbital) cortical volumes and PPI values in schizophrenia patients [24].

However, according to the present results, at least in some schizophrenia cases, an involvement of factors other than gating in cognitive deficits seems supported, since our patients showed cognitive but not PPI deficits. This has some previous support from studies on the association between cortical deficits and neurocognition. We reported, in an entirely different schizophrenia sample, a significant association between processing speed deficits and frontal hypometabolism, as well as between working memory performance and prefrontal structural deficit [31]. In the same direction, it has been reported that changes over time in prefrontal perfusion were associated with an improvement in working memory scores of schizophrenia patients [40].

Our study has limitations; notably, in the number of subjects. Furthermore, age differences between the patients and controls might have contributed to the absence of differences in PPI between groups, although their possible influence was controlled statistically. It has been reported that younger subjects in the middle age group may have lower PPI values [7], but our patients and controls were within the same age range as in that study. The difference in ages between these groups may have affected the comparisons between patients and controls, but not the within-group correlations with the cognitive scores.

The use of a single value of prepulse intensity and a single value of stimulus onset asynchrony may also be regarded as a limitation, since variations of the prepulse, both in intensity and time, are important in PPI measurements, though optimum values differ between sexes [26] and between controls and patients of several pathologies [5]. Nonetheless, to maintain the same experimental paradigm in all the subjects, a single value of prepulse intensity and a single value of stimulus onset asynchrony have been used in the present study, and therefore compliance in the patients is also necessary. Another limitation is the non-statistically significant difference in the number of males and females in the patient and control groups. However, sex was also included as a covariate in the between-group comparisons, and when we compared the male patients and the male controls, the differences remained the same. Additionally, this difference in distribution again would not affect the correlative within-subject analyses. Related to this, changes along the menstrual period within the same female subjects may influence PPI values [19, 38], and we did not control for the time of the menstrual cycles in the determination of PPI in female patients and controls. Finally, PPI and neurocognitive measurements were not conducted on the same day, and hence the clinical state may not have been the same. This may have contributed to the lack of association between PPI and cognitive parameters. However, this procedure is likely to result in better collaboration in cognitive testing in comparison to studying more acutely psychotic patients and will not hamper the cognitive performance of schizophrenic patients.

In conclusion, we failed to detect any association between this parameter and cognitive deficits in chronic schizophrenia patients.

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