Neuropsychological correlates of P50 sensory gating in patients with schizophrenia

Eva María Sánchez-Morla, José Luis Santos, Ana Aparicio, María Ángeles García-Jiménez, Carmen Soria, Celso Arango

Department of Psychiatry, Hospital Virgen de la Luz, Cuenca, Spain
Department of Psychiatry, Hospital Universitario de Guadalajara, Guadalajara, Spain
Neuropsychology Unit, Hospital Virgen de la Luz, Cuenca, Spain
Child and Adolescent Department of Psychiatry, ISGM, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, Madrid, Spain
School of Medicine, University of Alcalá, Madrid, Spain

Abstract

Impaired inhibition of P50 cerebral evoked response is one of the best validated endophenotypes in schizophrenia. There are controversial data on the relationship between P50 evoked potential deficit and measures of cognitive function in schizophrenia. A comprehensive clinical and neuropsychological assessment plus an evaluation of P50 sensory gating was performed in 160 schizophrenia patients and 64 controls. Neurocognitive scores from each cognitive domain were converted to demographically-adjusted T-scores (age, gender, and years of education) for all study participants. The relationship between P50 and neurocognitive variables was assessed via parametric and nonparametric correlations and categorical strategies: we compared neuropsychological test scores in patients and controls in the lowest P50 quartile vs. the highest. Controls had better performance than schizophrenia patients in all cognitive domains. Schizophrenia patients had significantly higher P50 ratios than controls, and no significant correlation was found between P50 gating measures and neuropsychological test scores in schizophrenia patients or healthy controls. Moreover, no differences in neurocognitive performance were found between subjects in the lowest P50 ratio quartile vs. the highest in healthy controls or patients with schizophrenia. We concluded that there is no evidence of an association between P50 ratio and cognitive measures in schizophrenia patients, and this seems to be also the case in healthy controls.

Keywords: P50, Schizophrenia, Cognition, Evoked potential recordings, Neuropsychological measures

1. Introduction

P50 wave is a preattentional component of the middle latency auditory evoked potentials (MLAEPs) recorded about 50 ms after the presentation of an auditory stimulus. MLAEPs decrease in amplitude when a second stimulus (S2), identical to the first stimulus (S1), is delivered about 500 ms later (Turetsky et al., 2007). This amplitude suppression of the wave evoked by the second stimulus (S2) reflects a sensory gating mechanism aimed at protecting against information overload (Braff and Geyer, 1990). Individuals with schizophrenia are known for having relatively less suppression of P50 amplitudes which has been related to the inability of the central nervous system to filter irrelevant sensory inputs (Adler et al., 1982). A P50 deficit suggests that there is an abnormality that affects early stages of information processing (Boutros et al., 2004). Subsequent studies have confirmed that P50 suppression deficits are already present in early stages of schizophrenia (Myles-Worsley et al., 2004; Brockhaus-Dumke et al., 2008a; Hong et al., 2009), in both acutely ill and more stable schizophrenia outpatients (Bramon et al., 2004; de Wilde et al., 2007; Patterson et al., 2008; Thaker, 2008) as well as in their first degree relatives (Olincy et al., 2010; Turetsky et al., 2012). The majority of studies have failed to demonstrate a significant relationship between P50 sensory gating and clinical symptoms (Adler et al., 1990; Jin et al., 1998; Boutros et al., 2004; Potter et al., 2006; Boutros et al., 2009; Santos et al., 2010).

Despite the fact that sensory gating as described by Venables (1964) was closely related to the phenomenon of cognitive impairment, in some patients who could not inhibit irrelevant stimuli and were overloaded by the environment, the reality is that few studies have examined whether there is any relationship between P50 and different domains of neuropsychological performance in patients with schizophrenia. P50 suppression abnormalities have been related to attention deficits assessed by the Gordon Diagnostic System version of the Continuous Performance Test (Erwin et al., 1998) and other attention tests (Cullum et al., 1993). Measures of processing speed have also been linked to P50 gating (Erwin et al., 1998). However, it is unclear whether P50 suppression deficits are linked to poorer performance in working memory and executive tests. Thus, correlation was found between P50 ratio and digit span backward (Cullum et al., 1993) although this finding could not be replicated (Erwin et al., 1998). P50 gating deficits have not been related to
measures of executive function (Erwin et al., 1998; Thoma et al., 2003, 2004), and verbal or visual explicit memory (Cullum et al., 1993; Erwin et al., 1998; Hsieh et al., 2004). Some limitations of previous studies is their relatively small sample size with reduced statistical power and use of different of P50 ratio measures (Fuerst et al., 2007; Dalecki et al., 2012).

The purpose of the present study was to examine the relationship between neuropsychological measures and P50 abnormalities in a large sample of stable outpatients with schizophrenia. It was hypothesized that when schizophrenia patients were divided into high- and low-P50 abnormality groups, the high-abnormality group (high P50 ratio) would show relatively greater and selective deficits on neuropsychological measures.

2. Method

2.1. Patients

We recruited 160 outpatients, ages 18 to 55, with a diagnosis of schizophrenia according to the Structured Clinical Interview for DSM-IV. All patients were medicated with antipsychotics and clinically stabilized for at least the three months preceding the assessment. Exclusion criteria were: 1) severe medical or neurological disease that can cause neuropsychological deterioration; 2) mental retardation; 3) history of substance abuse or dependence during the previous 2 years; 4) history of electroconvulsive therapy; 5) history of head injury with loss of consciousness; 6) less than six years of education.

2.2. Control subjects

The control group included 64 healthy volunteers, ages 18 to 55. All control subjects met the same exclusion criteria as patients, as well as the exclusion criteria of any Axis I diagnoses, and were from the same area and origin as the patient group (Hospital Virgen de la Luz, Cuenca, Spain). The SCID structured interview was administered to rule out a history of psychiatric illness. In addition, subjects with first-degree relatives diagnosed with bipolar disorder or schizophrenia, were excluded at the screening interview.

2.3. Neuropsychological assessment

A battery of 11 neurocognitive tests that provided 20 neuropsychological measurements was administered by trained personnel, who were blind to diagnosis and the research hypothesis. The neurocognitive tests were always given in the same sequence. The neuropsychological evaluation lasted about 3 h, interspersed with two rest periods to relieve fatigue. Tests were assigned to the following six cognitive domains: 1) processing speed: Trail Making Test part A (TMT-A), digit symbol of the Wechsler Adult Intelligence Scale Revised (WAIS-R), category verbal fluency test (animal naming); 2) verbal working memory: digits backward and letter-numbers of the Wechsler Memory Scale (WMS – III); 3) sustained attention: Degraded Stimulus Continuous Performance Test, Version 8.12; 4) verbal learning and memory: California Verbal Learning Test (CVLT); 5) visual memory: Rey–Osterreith Complex Figure Test (ROCFT); 6) executive function: Wisconsin Card Sorting Test (WCST), Stroop Test (interference), Trail Making Test part B (TMT-B), and Controlled Oral Word Association Test (COWAT). Neuropsychological domains and measurements were selected based on previous criteria (Heimrichs and Zakzanis, 1998; Schretlen et al., 2007; Nuechterlein et al., 2008).

2.4. Electrophysiological recordings

Evoked potentials were recorded the same day that the neuropsychological battery was performed. Three sets of 30 pairs of auditory clicks were delivered binaurally through ear-insert earphones with a peak intensity of 65 dB above the hearing threshold, with an interstimulus interval of 500 ms and an interpair interval of 10 s. A square wave pulse 0.1 ms in duration was amplified in the 20–12,000 Hz bandwidth and delivered. Recordings were obtained with a gold disc electrode affixed to the vertex and referenced to one ear. Electrode resistance was less than 10 kΩ. Two-channel Syn-nergy evoked potential equipment was used with bandpass filtered at 1–200 Hz. The electrooculogram (EOG) from the superior orbital ridge referenced to the lateral canthus was also recorded to detect ocular movement artifacts. The EEG and EOG channels were then screened for post-acquisition artifacts, and trials containing artifacts (± 50 μV EOG or EEG channel) were not included in the waveform averaging. The artifact-free epochs were averaged for each subject to obtain the P50 waves. The central channel was used because it provides the most prominent P50 gating (Nagamoto et al., 1989). The P50 component was identified using the same procedures previously reported (Sánchez-Morla et al., 2008, 2009b). P50 gating was defined as both P50 ratio (amplitude S2 / amplitude S1) and P50 difference (amplitude S1-amplitude S2).

2.5. Statistical analyses

Statistical analyses were done using IBM SPSS Statistics 19.0 for Windows. Neurocognitive scores from each cognitive domain were converted to demographically-adjusted T-scores (age, gender, and years of education) for all study participants, based on the normal subject scores. The general procedure for these adjustments has been used previously (Schretlen et al., 2007). The demographically-adjusted T-score distribution approximates a mean of 50 and a standard deviation of 10 for each cognitive measure. Global scores for cognitive domains were obtained by averaging the demographically-adjusted T-scores on each of the measures that are part of the domain.

The relationships between P50 (P50 ratio and P50 difference), and neuropsychological and clinical variables were assessed via parametric and nonparametric correlations and categorical (quartile split) strategies, as has been described elsewhere (Swerdlow et al., 2006). Thus, we compared neuropsychological test scores in patients and controls in the lowest P50 ratio quartile (quartile 1) vs. the highest (quartile 4).

Multivariate analysis of variance (MANOVA) was performed for all cognitive measures with diagnosis (patients groups and schizophrenia group) and P50 ratio quartile (lowest quartile and highest quartile) as inter-subject factors.

This study was approved by the Cuenca Hospital Independent Ethics Committee. All patients provided written informed consent before entering the study.

3. Results

The healthy control group and patients with schizophrenia differed in age, education, gender, and smoking status (Table 1).

When patients were classified according to P50 ratio, 38 patients were in the lowest quartile group and 39 in the highest quartile. Sixteen healthy controls were in the lowest P50 ratio quartile and another 16 in the highest quartile. Likewise, we did not observe any significant differences in the demographic variables, either in patients or controls, using P50 ratio quartile as inter-subject factor.

3.1. Neurocognitive measures

The overall MANOVA (Pillai’s trace: 0.493; F(6,212):34.3; p<0.0001) indicated significant differences in neuropsychological function between patients with schizophrenia and the control group. Control subjects had better performance than schizophrenia patients in all cognitive domains (Table 1).
3.2. Neurophysiological measures (Table 1)

P50 could not be recorded in six patients with schizophrenia and three healthy subjects, and these subjects were not analyzed. Table 1 shows P50 measures by group. There was a significant main group effect on P50 ratio, after controlling for age, gender, education, and smoking status (F1,218 = 32.3; p < 0.0001). Compared with control subjects, schizophrenia patients had higher P50 ratios. There were no significant differences between schizophrenia patients and healthy subjects. We identified a P50 gating deficit in schizophrenia patients compared with control subjects. This deficit in sensory gating is robust with a standardized effect size of 0.82. Our result is in agreement with many previous studies describing P50 gating deficits in patients with schizophrenia (Adler et al., 2010).

Table 2

<table>
<thead>
<tr>
<th>Measure</th>
<th>Quartile 1 Mean (SD)</th>
<th>Quartile 4 Mean (SD)</th>
<th>ANOVA P</th>
<th>Correlations (Spearman)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. categories</td>
<td>33.12 (16.07)</td>
<td>36.01 (18.44)</td>
<td>0.401</td>
<td>0.001*</td>
</tr>
<tr>
<td>% perseverative errors</td>
<td>34.68 (32.67)</td>
<td>32.67 (20.71)</td>
<td>0.994</td>
<td>0.005*</td>
</tr>
<tr>
<td>TMT-A</td>
<td>35.37 (23.46)</td>
<td>33.31 (23.31)</td>
<td>0.774</td>
<td>0.029*</td>
</tr>
<tr>
<td>TMT-B</td>
<td>20.78 (29.11)</td>
<td>21.63 (29.87)</td>
<td>0.902</td>
<td>0.001*</td>
</tr>
<tr>
<td>Stroop (interference)</td>
<td>37.55 (10.48)</td>
<td>38.80 (10.67)</td>
<td>0.457</td>
<td>0.008*</td>
</tr>
<tr>
<td>Verbal fluency (categories)</td>
<td>37.21 (11.18)</td>
<td>37.90 (9.35)</td>
<td>0.349</td>
<td>0.008*</td>
</tr>
<tr>
<td>Verbal fluency: letter</td>
<td>39.1 (13.11)</td>
<td>39.0 (11.8)</td>
<td>0.954</td>
<td>0.009*</td>
</tr>
<tr>
<td>Span digits forward</td>
<td>42.51 (9.37)</td>
<td>45.51 (8.13)</td>
<td>0.190</td>
<td>0.016*</td>
</tr>
<tr>
<td>Span digits backward</td>
<td>40.21 (12.16)</td>
<td>44.71 (9.14)</td>
<td>0.062</td>
<td>0.023*</td>
</tr>
<tr>
<td>Letter and number</td>
<td>38.02 (11.71)</td>
<td>38.80 (15.21)</td>
<td>0.600</td>
<td>0.127*</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>24.8 (12.92)</td>
<td>28.5 (15.4)</td>
<td>0.270</td>
<td>0.020*</td>
</tr>
<tr>
<td>CVLT learning (trials 1–5)</td>
<td>32.57 (11.28)</td>
<td>35.95 (11.94)</td>
<td>0.264</td>
<td>0.225*</td>
</tr>
<tr>
<td>CVLT, Free recall (short)</td>
<td>33.87 (11.00)</td>
<td>36.21 (17.31)</td>
<td>0.557</td>
<td>0.191*</td>
</tr>
<tr>
<td>CVLT, Free recall (long)</td>
<td>31.9 (12.6)</td>
<td>35.1 (12.2)</td>
<td>0.275</td>
<td>0.056*</td>
</tr>
<tr>
<td>Recognition: discriminability</td>
<td>34.67 (17.9)</td>
<td>35.80 (17.7)</td>
<td>0.834</td>
<td>0.223*</td>
</tr>
<tr>
<td>ROCFT recall (immediate)</td>
<td>29.01 (13.5)</td>
<td>33.98 (10.13)</td>
<td>0.048</td>
<td>0.212*</td>
</tr>
<tr>
<td>ROCFT recall (delayed)</td>
<td>29.4 (13.5)</td>
<td>34.4 (10.1)</td>
<td>0.076</td>
<td>−0.183*</td>
</tr>
<tr>
<td>CPT, Hits</td>
<td>35.30 (14.4)</td>
<td>35.30 (15.8)</td>
<td>0.898</td>
<td>0.118*</td>
</tr>
<tr>
<td>CPT, Sensitivity A</td>
<td>43.49 (13.3)</td>
<td>42.25 (13.9)</td>
<td>0.713</td>
<td>0.082*</td>
</tr>
<tr>
<td>CPT, Reaction time</td>
<td>42.21 (13.80)</td>
<td>38.79 (15.5)</td>
<td>0.844</td>
<td>−0.032*</td>
</tr>
</tbody>
</table>

TMT: Trail Making Test. CVLT: California Verbal Learning Test. ROCFT: Rey–Osterreith Complex Figure Test. CPT: Continuous Performance Test.

* p not significant.

Please cite this article as: Sánchez-Morla, E.M., et al., Neuropsychological correlates of P50 sensory gating in patients with schizophrenia, Schizophr. Res. (2012), http://dx.doi.org/10.1016/j.schres.2012.10.017
little correlation with clinical and cognitive measures. A more refined method in the frequency domain analyses that measure gating responses to S1 and S2 in single trials is likely to provide more information about the relationship between P50 gating and the observed cognitive impairments in schizophrenia syndrome.

Role of the funding source
Funding for this study was provided by a research grant (03016-01) provided by the Institute of Health of the Castilla La Mancha Regional Executive in Spain; this Institute of Health had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors
JLS and EMSM designed the study and wrote the protocol. JLS, EMSM and CA managed the literature searches and analyses. JLS, EMSM, MGJ, CS and AA selected the sample and evaluated patients. JLS undertook the statistical analysis. JLS, CA and EMSM wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
JLS has received grants and served as consultant, advisor or speaker for the following entities Eli Lilly, Janssen-Cilag, Lundbeck, Pfizer and Otsuka. CA has been a consultant to or has received honoraria or grants from Abbot, AMGEN, AstraZeneca, Bristol-Myers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Instituto de Salud Carlos III, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier and Schering Plough. The other authors declare that they have no conflicts of interest.

Acknowledgment
This work was supported by a research grant (03016-01) provided by the Institute of Health of the Castilla La Mancha Regional Executive in Spain and by a research grant of Instituto de Salud Carlos III (PI 10/01215).

References
Bozikas, et al., 2011), although high heterogeneity in effect size has been pointed out (Bramon et al., 2004). Also, according to previous studies, subjects with schizophrenia showed widespread neurocognitive deficits affecting all neurocognitive domains (Kurtz, 2005; Sánchez-Morla et al., 2009a; Reichenberg, 2010).

Our data does not support the results obtained in previous studies reporting that the P50 gating deficit was associated with impairment in cognitive measures (Cullum et al., 1993; Erwin et al., 1998), although negative data similar to this study have been also reported (Thoma et al., 2003, 2004; Louchart de la Chapelle et al., 2005). These previous studies were conducted with small sample sizes and reduced neurocognitive batteries, which limit their findings and may explain the discrepancy with the present results. In keeping with our results, other neuropsychological studies that have examined sensorimotor gating assessed by prepulse inhibition (PPI), in a large sample of patients with schizophrenia, found no relationship between PPI deficits and performance on cognitive tests (Swerdlov et al., 2006). Thus, evidence suggests that the brain circuitry responsible for deficits in sensorimotor gating during the preattentive phase of information processing does not contribute via a strong path to neuropsychological deficits in patients with schizophrenia. However, it is possible that sensory gating at later stages than 50 ms might be related to cognitive dysfunction in schizophrenia, as has been suggested when N100 gating is evaluated (Boutros et al., 2009; Lijffijt et al., 2009; Mazhari et al., 2011). Moreover, we cannot exclude the possibility that the lack of correlation between sensory gating failure and cognitive deficits in patients with schizophrenia may be due to the fact that the measure of evoked response is based on averaging across trials (Hong et al., 2012). Recent studies using spectral frequency analysis in single trials have provided additional information about auditory sensory processing in the schizophrenia population (Brockhaus-Dumke et al., 2008b; Hong et al., 2008; Brenner et al., 2009; Mathiak et al., 2011; Hong et al., 2012).

The present study has a number of limitations. It was cross-sectional, with chronic schizophrenia patients, although neurocognitive deficits and P50 gating deficit seem to have a stable course, and both have already been reported in early stages of the disorder (Myles-Worsley et al., 2004; Brockhaus-Dumke et al., 2008a; Hong et al., 2009; Bozikas and Andreou, 2011). A second limitation is that the schizophrenia participants were all medicated with antipsychotics. It is known that antipsychotics can affect the cognitive domains (Woodward et al., 2005; Nagamoto et al., 1999; Becker et al., 2004), seem to remedy sensory gating deficits in schizophrenia patients (Arango et al., 2003; Adler et al., 2004). In addition, no differential impact of antipsychotic medications has been found on P50 gating (Hong et al., 2009; Sánchez-Morla et al., 2009a, 2009b; Su et al., 2012). Therefore, the impact of antipsychotic treatment on P50 seems to be limited, at most. Finally, patients and control group differed with respect some variables such as age, years of education, or gender distribution. Therefore, we used regression-based adjustments for demographic variables, following the procedure established by Schretlen et al. (2007). This approach standardizes the difference between an individual’s actual test scores and those predicted on the basis of demographic characteristics. This approach obviates the need to match patient and control groups on demographic variables because their influence is statistically “removed” from each individual’s test scores (Heaton et al., 2004; Schretlen et al., 2007).

In conclusion, we have not found a relationship between neuropsychological performance and P50 gating in patients with schizophrenia or healthy subjects. Paradoxically, one of the most robust neurophysiological endophenotypes identified in schizophrenia has


Please cite this article as: Sánchez-Morla, E.M., et al., Neuropsychological correlates of P50 sensory gating in patients with schizophrenia, Schizophr. Res. (2012), http://dx.doi.org/10.1016/j.schres.2012.10.017