Physical Features (Electrophysiology) - P50

Introduction

Schizophrenia may be associated with cognitive and perceptual deficits. These may be caused by an inability to “gate” or inhibit irrelevant sensory information, which may lead to a conscious information overload.

The P50 event-related potential is measured using electroencephalogram (EEG) technology, and is interpreted as a physiological substrate for a sensory-gating deficit [1], by measuring the inhibition of a response following a prior exposure.

In this paradigm, two auditory clicks are presented, separated by a 500ms interval. The first click generates a normal auditory response, while the second click should generate an attenuated response due to sensory-gating [2]. The P50 ratio is measured as the difference in amplitude between the first and second clicks. If the second click does not generate a blunted response, this is interpreted as a deficit in sensory gating [3, 4].

Alterations in the P50 gating mechanism is proposed to have potential as a marker for schizophrenia [2].

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. As part of a wider search for all topics included in the library, reviews on P50 ERPs for schizophrenia were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. The decision to include or exclude reviews was conducted in duplicate by two independent reviewers with any disagreements settled by discussion. All quality assessments and data extraction have been completed in duplicate by two reviewers who were not masked to review authors.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (formerly the QUOROM statement) which describes a preferred way to present a meta-analysis [5]. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. Reviews rated as having a high possibility of reporting bias have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomized controlled trials (RCT) may be downgraded to moderate, low or very low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be
downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[6]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.

Results

See table below for a detailed summary of the available evidence pertaining to P50 ERPs. We found five systematic reviews that met our inclusion criteria [1, 3, 4, 7, 8]. One review was excluded, which was not a systematic review [2].

See PRISMA checklist for quality assessments of review reporting.

Conclusions

- Moderate to high quality evidence suggests the P50 ratio is significantly increased in schizophrenia and in relatives of patients with schizophrenia. Patients show a blunted response to stimulus one and a heightened response to stimulus two indicating reduced sensory gating.
- Moderate quality evidence suggests P50 latency is not altered in patients with schizophrenia.
- High quality evidence suggests no difference in P50 ratio following second generation antipsychotic treatment. Moderate quality evidence also suggests no difference in P50 ratios following first generation antipsychotic treatment.
### Physical Features (Electrophysiology) - P50

#### Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S.

**Meta-analysis of the P300 and P50 waveforms in schizophrenia**


[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Comparison of P50 ERP ratio and latency in schizophrenia vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large sample size, precise, direct, inconsistent) suggests P50 ratio is increased in schizophrenia, although P50 latency is not different</td>
</tr>
</tbody>
</table>

**P50 activity**

- 20 studies, N = 822
- **P50 ratio**
  - Large effect size suggests significantly increased P50 ratio in schizophrenia
    - $d = -1.56$, 95%CI -2.05 to -1.06, $p < 0.001$
- **P50 latency**
  - No difference in P50 latency
    - $d = 0.08$, 95%CI -0.09 to 0.25, $p = 0.34$

**Consistency in results**

- Significant heterogeneity reported for ratio, $p < 0.001$. Consistent for latency, $p = 0.24$

**Precision in results**

- Precise for both outcomes

**Directness of results**

- Direct comparison of P50 activity in schizophrenia and control

#### Chang WP, Arfken CL, Sangal MP, Boutros NN.

**Probing the relative contribution of the first and second responses to sensory gating indices: a meta-analysis**

Psychophysiology 2011; 48:980-992

[View review abstract online](#)
### Physical Features (Electrophysiology) - P50

<table>
<thead>
<tr>
<th>Comparison 1</th>
<th>Comparison of amplitude of stimulus 1 [S1] and stimulus 2 [S2], and ratio between S1 and S2 in people with schizophrenia vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (large sample size, precise, direct, inconsistent) suggests the P50 ratio is increased in people with schizophrenia, including a blunted response to stimulus one (relative to controls) and a heightened response to stimulus two (relative to controls)</td>
</tr>
</tbody>
</table>

### P50 activity

58 comparisons (35 studies), N = 3166

**P50 S1 amplitude**

- Small effect size suggests significantly reduced amplitude in schizophrenia
  
  \[ d = -0.19, \ 95\%CI \ -0.29 \ to \ -0.10 \]
  \[ Q = 116.69, \ p < 0.0005, I^2 = 51.15\% \]

**P50 S2 amplitude**

- Medium effect size suggests significantly increased amplitude in schizophrenia
  
  \[ d = 0.65, \ 95\%CI \ 0.48 \ to \ 0.81 \]
  \[ Q = 344.61, \ p < 0.0005, I^2 = 83.46\% \]

**P50 S1 ratio**

- Large effect size suggests significantly increased P50 ratio in schizophrenia
  
  \[ d = 0.93, \ 95\%CI \ 0.75 \ to \ 1.10 \]
  \[ Q = 368.74, \ p < 0.0005, I^2 = 84.54\% \]

*Authors report substantial funnel plot asymmetry indicating a publication bias against small or null effects*

<table>
<thead>
<tr>
<th>Consistency in results(\dagger)</th>
<th>Inconsistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision in results(\dagger)</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness of results(\dagger)</td>
<td>Direct comparison of P50 activity</td>
</tr>
</tbody>
</table>
**Physical Features (Electrophysiology) - P50**

*de Wilde OM, Bour LJ, Dingemans PM, Koelman JH, Linszen DH, Koelman JHTM.*

**A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups**

**Schizophrenia Research** 2007; 97(1-3):137-151

[View online review abstract](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison 1</td>
<td>Comparison of P50 ERP ratio in schizophrenia vs. healthy controls</td>
</tr>
</tbody>
</table>

**Summary of evidence**

- Moderate to high quality evidence (large sample size, consistent, direct, imprecise) suggests P50 ratio is significantly increased in schizophrenia.
- Authors report that methodological considerations make comparison across studies difficult.

**P50 activity**

**P50 ratio**

- 34 studies, N = 1577
- Large effect size suggests increased P50 ratio in schizophrenia
- $d = 1.28$, $SD = 0.72$, 95%CI -0.13 to 2.69
- $FSN = 183.6$, $OL\% = 34.7\%$

**Subgroup analysis: Combined effect size excluding studies from one over-represented research group**

- Large effect size suggesting increased P50 ratio in schizophrenia
- $d = 0.85$, $SD = 0.42$

This difference also accounted for variation in effect size related to subject test position (laying vs. sitting) and intensity effects.

**Consistency in results** Consistent

**Precision in results** Imprecise

**Directness of results** Direct

**Comparison 2** Comparison of P50 ERP ratio in relatives of patients with schizophrenia vs. healthy controls
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<table>
<thead>
<tr>
<th>Summary of evidence</th>
<th>Moderate to high quality evidence (large sample size, consistent, direct, unable to assess precision) suggests P50 ratio is significantly increased in relatives of patients with schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P50 activity</strong></td>
<td></td>
</tr>
<tr>
<td>6 studies, N = 611</td>
<td></td>
</tr>
<tr>
<td><em>P50 ratio</em></td>
<td></td>
</tr>
<tr>
<td>Large effect size suggests increased P50 ratio in relatives of patients with schizophrenia, compared to controls</td>
<td></td>
</tr>
<tr>
<td>( d = 0.85, \text{SD} = 0.42 )</td>
<td></td>
</tr>
<tr>
<td>FSN = 19.5</td>
<td></td>
</tr>
<tr>
<td><strong>Consistency in results</strong></td>
<td>Consistent</td>
</tr>
<tr>
<td><strong>Precision in results</strong></td>
<td>No measure of precision reported</td>
</tr>
<tr>
<td><strong>Directness of results</strong></td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Patterson JV, Hetrick WP, Boutros NN, Jin Y, Sandman C, Stern H, Potkin S, Bunney WE, Jr.**

**P50 sensory gating ratios in schizophrenics and controls: a review and data analysis**

*Psychiatry Research 2008; 158(2):226-247*

[View review abstract online](#)

<table>
<thead>
<tr>
<th><strong>Comparison 1</strong></th>
<th>Comparison of P50 ERP ratio in schizophrenia vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of evidence</strong></td>
<td>Low to moderate quality evidence (very large samples, inconsistent, imprecise, direct) suggests P50 ratios are increased in schizophrenia</td>
</tr>
</tbody>
</table>

**Difference in P50 ratio**

84 studies, N = 3420

Observed ratio range from 56-158%, mean 79.9%, SD = 24.3 in schizophrenia
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Observed ratio range 9-73.4%, mean 38.8%, SD = 15.3 in controls
40% of controls had ratios within 1 SD of patients

*Meta-analysis of subset of studies reporting sufficient data to combine*

39 studies, N unclear
Average difference in P50 ratio, WMD = 45.8%, 95%CI 38.2 to 53.4
Cochran’s Q = 406.9, p < 0.001

*Subgroup analyses: moderator variables*

P50 ratio difference was moderated by filter settings, the observed ratio was smaller with 0.8Hz and 10Hz filters than for 30Hz filters
No associations were reported for click intensity, age, sex, or delivery mode

<table>
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<th>Consistency in results</th>
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<tbody>
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<td>Imprecise</td>
</tr>
<tr>
<td>Directness of results</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Su L., Cai Y, Wang L, Shi S.**

**Various effects of antipsychotics on P50 sensory gating in Chinese schizophrenia patients: a meta-analysis**

*Psychiatria Danubina 2012; 24(1):44-50*

[View review abstract online](#)

**Comparison 1**
Comparison of P50 ERP ratio in Chinese people with schizophrenia before and after treatment with various antipsychotics

**Summary of evidence**
High quality evidence (consistent, precise, direct,) suggests no difference in P50 ratios following second generation antipsychotic treatment. Moderate quality evidence (small sample) also suggests no difference in P50 ratios following first generation antipsychotic treatment

**Difference in P50 ratio**

Overall (all medications) – no difference in P50 ratio
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<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>d</th>
<th>95%CI</th>
<th>p</th>
<th>Q</th>
<th>p</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation antipsychotics</td>
<td>6</td>
<td>285 at follow-up</td>
<td>0.08</td>
<td>-0.08 to 0.25</td>
<td>0.30</td>
<td>2.81</td>
<td>0.81</td>
</tr>
<tr>
<td>Second generation antipsychotics</td>
<td>6</td>
<td>229 (209 at follow-up)</td>
<td>0.05</td>
<td>-0.14 to 0.24</td>
<td>0.58</td>
<td>0.43</td>
<td>0.79</td>
</tr>
<tr>
<td>Mixed first and second generation antipsychotics</td>
<td>1</td>
<td>42 (32 at follow-up)</td>
<td>0.13</td>
<td>-0.33 to 0.59</td>
<td>0.57</td>
<td>0.13</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Consistency in results | Consistent where applicable  
Precision in results | Precise  
Directness of results | Direct

Explanation of acronyms

CI = Confidence Interval, d = Cohen’s d and g = Hedges’ g = standardized mean differences (see below for interpretation of effect sizes), ERP = event-related potential, FSN = fail-safe N, Hz = Hertz unit (number of cycles per second), N = number of participants, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, SD = standard deviation, vs. = versus, WMD = weighted mean difference
Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials which are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.[9]

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomized trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study’s mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large treatment effect[9]. Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A large effect is considered if RR > 2 or < 0.5 and a very large effect if RR > 5 or < 0.2[10]. InOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardized (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardized
regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

† Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. $I^2$ is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. $I^2$ can be calculated from $Q$ (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left( \frac{Q - df}{Q} \right) \times 100\%$$

‡ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[10].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Many thanks to Dr Juanita Todd for reviewing this summary of evidence

School of Psychology, University of Newcastle
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References