TECHNICAL COMMENTARY

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P50 Event-related potential

Introduction

Some theories suggest that schizophrenia is associated with cognitive and perceptual deficits, which may be manifested as an inability to "gate" or inhibit irrelevant sensory information, ultimately leading to conscious information overload. The P50 event-related potential is interpreted as a physiological substrate for this deficit. In this paradigm, paired auditory clicks are presented, separated by a 500ms interval. A positive brain potential measured maximally over the vertex is observed using electroencephalogram (EEG) technology, with the vertex 50ms following the stimulus. The first click initiates or conditions the inhibition, while the second (test) click indexes the strength of the inhibition. P50 ratio is quantified as the amplitude of the response to the second click divided by the first. The absence of a reduced response to the second stimulus is interpreted as a failure of inhibitory mechanisms, postulated to represent a defect in sensory gating. Alterations in the P50 gating mechanism is proposed to have potential candidacy as an endophenotype (closer to genetic link than phenotype) for schizophrenia.

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. Reviews 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. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked 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 randomised controlled trials (RCTs) may be downgraded to moderate or 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)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

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Results

We found five systematic reviews that met our inclusion criteria[3-7].

- Moderate to high quality evidence suggests a large effect of increased P50 ratio in people with schizophrenia, and in relatives of people with schizophrenia, when compared to controls. P50 latency was not altered.
- There was a small decrease in S1 amplitude, and a medium increase in S2 amplitude.
- Moderate to high quality evidence suggests no differences in P50 ratios before vs. after treatment with antipsychotics in Chinese people with schizophrenia.

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

Meta-analysis of the P300 and P50 waveforms in schizophrenia

Schizophrenia Research 2004; 70(2-3): 315-329

View review abstract online

Comparison	**Comparison of P50 ratio and latency in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests P50 ratio is increased in people with schizophrenia, and P50 latency is not different.**
P50 activity	
Large effect size suggests significantly increased P50 ratio in people with schizophrenia; 20 studies, N = 822, *d* = -1.56, 95%CI -2.05 to -1.06, *p* < 0.001 *No significant difference in P50 latency;* 20 studies, N = 822, *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

Chang W, 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 online review abstract

Comparison	**Comparison of S1 amplitude, S2 amplitude, and S2/S1 ratio in people with schizophrenia vs. healthy controls.**

Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small effect of decreased S1 amplitude, a medium effect of increased S2 amplitude, and a large effect of increased S2/S1 ratio in patients with schizophrenia compared to controls. Note that the S2/S1 ratio result may be subject to publication bias.**
P50 activity	
Significant, small reduction in S1 amplitude (initial response) in patients compared to controls; 58 effect sizes, N = 2821, *d* = -0.19, 95%CI -0.29 to -0.10, $p < 0.05$, OL% 85.74%, I^2 51.15%, p = 0.0005 *Significant, medium increase in S2 amplitude (repeated stimuli) in patients compared to controls;* 58 effect sizes, N = 2821, *d* = 0.65, 95%CI 0.48 to 0.81, $p < 0.05$, OL% 59.62%, I^2 83.46%, p = 0.0005 *Significant, large increase in S2/S1 ratio in patients compared to controls;* 58 effect sizes, N = 2821, *d* = 0.93, 95%CI 0.75 to 1.10, $p < 0.05$, OL% 47.37%, I^2 84.54%, p = 0.0005 Funnel plot for S2/S1 ratio showed possible publication bias	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

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

Comparison 1	**Comparison of P50 ratio in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests P50 ratio is significantly increased in people with schizophrenia.**
P50 ratio	

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Large effect size suggests increased P50 ratio in schizophrenia; 34 studies, N = 1577, *d* = 1.28, 95%CI -0.13 to 2.69, FSN = 183.6, OL% 34.7 Similar reports were reported after excluding studies from one over-represented research group *Large effect size suggesting increased P50 ratio in schizophrenia;* *d* = 0.85, SD = 0.42	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Comparison of P50 ratio in relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, unable to assess precision, direct) suggests P50 ratio is significantly increased in relatives of people with schizophrenia.**
P50 ratio	
Large effect size suggests increased P50 ratio in relatives of people with schizophrenia; 6 studies, N = 611, *d* = 0.85, SD = 0.42, FSN = 19.5	
Consistency in results	Consistent
Precision in results	No measure of precision is reported.
Directness of results	Direct

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

Comparison	**Comparison of P50 ERP ratio in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests P50 ratios are increased in people with schizophrenia.**
P50 ratio	
84 studies, N = 3420 Observed ratio range from 56-158%, mean 79.9%, SD = 24.3 in schizophrenia 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, WMD = 45.8%, 95%CI 38.2 to 53.4, Q = 406.9, $p < 0.001$ 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.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

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	**Comparison of P50 measures pre- to post-antipsychotic medication in Chinese people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (medium to large sample, consistent, imprecise, direct) suggests no differences in P50 ratios before vs. after treatment with antipsychotics.**

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P50 ratio	
No significant differences in P50 ratio between baseline and follow-up (4 - 12 weeks); 6 studies, N = 315 at baseline, 285 at follow-up, *d* = 0.08, 95%CI -0.08 to 0.25, *p*=0.30, I^2=0%, *p* = 0.95 Subgroup analysis showed no differences in results between first and second generation antipsychotics.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *d* or *g* = Cohen's d and g = Hedges' g = standardised mean differences (see below for interpretation of effect sizes), FSN = fail-safe N, Hz = Hertz unit (number of cycles per second), I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OL% = percentage of overlap in the P50 measure distribution between schizophrenia patients and healthy controls, *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

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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 that 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[8].

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† 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 randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised 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 medium effect, and 0.8 and over represents a large treatment effect[8]. Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that 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 medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[9]. lnOR 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 unforseen 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. Unstandardised (*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. Standardised 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) that 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.

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