TECHNICAL COMMENTARY

P300 Event-related potential

Introduction

The P300 wave is an event-related brain potential (ERP) measured using electroencephalography (EEG). P300 refers to a spike in activity approximately 300ms following presentation of the target stimulus, which is alternated with standard stimuli to create an 'oddball' paradigm, which is most commonly auditory. In this paradigm, the subject must respond only to the infrequent target stimulus rather than the frequent standard stimulus. The amplitude of the P300 response is proportional to the amount of attentional resource devoted to the task and the degree of information processing required, while the latency is considered a measure of stimulus classification speed, unrelated to behavioural response time.

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 that describes a preferred way to present a meta-analysis[1]. Reviews with 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 to 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).

Results

We found six systematic reviews that met our inclusion criteria[3-8].

- Moderate to high quality evidence suggests medium to large effects of reduced P300 amplitude and increased/delayed P300 latency in people with schizophrenia, and in

non-psychotic relatives of people with schizophrenia, when compared to controls.

- When comparing people with schizophrenia to non-psychotic relatives, there is a small effect of greater reduction in P300 amplitude and increased latency in people with schizophrenia.

- There was a greater reduction in amplitude in medication-free patients (large effect) than in medicated patients (medium effect), while latency increases were similar (medium effects).

- Moderate quality evidence suggests the highest magnitude of difference was reported in electrodes corresponding to the parietal cortex, and was lateralised to the left hemisphere, with highest magnitude around the left temporal lobe. Increases in task difficulty may increase the effect size.

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 P300 ERP amplitude and latency in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests P300 amplitude is reduced and latency is increased in people with schizophrenia. There was a greater reduction in amplitude in medication-free patients than in medicated patients.**

P300 activity

Measured as the mean response of parietal and central electrodes

Significant, medium-sized effect of reduced amplitude in people with schizophrenia;

46 studies, N = 2694, *d* = 0.78, 95%CI 0.65 to 1.05, *p* < 0.001

Significant, medium-sized effect of increased latency in people with schizophrenia;

46 studies, N = 2694, *d* = -0.57, 95%CI -0.75 to -0.38, *p* < 0.001

Significant, large effect of reduced amplitude in medication-free patients;

11 studies, N = 516, *d* = 1.23, 95%CI 0.86 to 1.60, *p* < 0.001

Significant, small effect of increased latency in medication-free patients;

11 studies, N = 516, *d* = -0.48, 95%CI -0.80 to -0.15, *p* = 0.004

Meta-regression identified that there was a greater reduction in amplitude in medication-free patients than in medicated patients; *p* = 0.03.

Consistency in results[‡]	Significant inconsistency is reported.
Precision in results[§]	Precise
Directness of results[∥]	Direct

Bramon E, McDonald C, Croft RJ, Landau S, Filbey F, Gruzelier JH, Sham PC, Frangou S, Murray RM

Is the P300 wave an endophenotype for schizophrenia? A meta-analysis and a family study

View online review abstract

Comparison 1	**Comparison of P300 ERP amplitude and latency in non-psychotic relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests P300 amplitude is significantly reduced, and latency is significantly increased in non-psychotic relatives of people with schizophrenia.**

P300 activity

Measured as the mean response of parietal and central electrodes

Significant, medium-sized effect of reduced P300 amplitude in relatives;

11 studies, N = 985, d = 0.61, 95%CI 0.30 to 0.91, p < 0.001

Significant, medium-sized effect of increased P300 latency in relatives;

11 studies, N = 985, d = -0.50, 95%CI -0.88 to -0.13, p = 0.009

Consistency in results	Significant between-study heterogeneity reported for amplitude, p < 0.001, and for latency, p = 0.02.
Precision in results	Precise for all outcomes.
Directness of results	Direct
Comparison 2	**Comparison of P300 ERP amplitude and latency in people with schizophrenia vs. non-psychotic relatives of people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, precise, direct) suggests a small effect of greater reduction in P300 amplitude and increased latency in people with schizophrenia compared to non-psychotic relatives.**

P300 activity

Measured as the mean response of parietal and central electrodes

Significant, small effect of greater reduction in P300 amplitude in patients than relatives; 9 studies, N = 579, *d* = 0.39, 95%CI 0.05 to 0.73, *p* = 0.03 *Significant, small effect of greater increase in latency in patients than relatives;* 9 studies, N = 579, *d* = -0.28, 95%CI -0.45 to -0.12, *p* < 0.01	
Consistency in results	Significant between-study heterogeneity reported for amplitude, *p* = 0.02, for latency, *p* < 0.01.
Precision in results	Precise for all outcomes.
Directness of results	Direct comparison of P300 amplitude and latency in non-psychotic relatives and controls.

Galderisi S, Mucci A, Volpe U, Boutros N

Evidence-based medicine and electrophysiology in schizophrenia

Clinical EEG & Neuroscience: Official Journal of the EEG & Clinical Neuroscience Society (ENCS) 2009; 40(2): 62-77

View review abstract online

Comparison	**Comparison of P300 amplitude, measured by qualitative spectral EEG in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a large effect of reduced P300 amplitude in people with schizophrenia.**
P300 amplitude	
Significant, large effect of reduced P300 amplitude in people with schizophrenia; 52 studies, N = 3073, *d* = -0.93, 95%CI -1.034 to -0.821, SE = 0.054, variance = 0.003	
Consistency in results	Authors report significant heterogeneity.
Precision in results	Precise
Directness of results	Direct

Jeon YW, Polich J

P300 asymmetry in schizophrenia: a meta-analysis

Psychiatry Research 2001; 104: 61-74

View review abstract online

Comparison	Comparison of P300 amplitude between topographical electrodes in people with schizophrenia vs. controls.
Summary of evidence	Moderate quality evidence (unable to assess sample size, mostly inconsistent, precise, direct) suggests a large effect of reduced P300 amplitude in people with schizophrenia compared to controls. This difference is of highest magnitude in the regions corresponding to the parietal cortex. The difference has higher magnitude in the left hemisphere, particularly around the left temporal lobe.

P300 amplitude

Frontal, central and parietal regions

Significant, large effect of reduced P300 amplitude in people with schizophrenia compared to controls;

19 studies, N not reported, d = 0.86, 95%CI 0.79 to 0.92, Q_w = 158.49, p = 0.000

Frontal

Significant, medium effect of reduced P300 in the frontal cortex of people with schizophrenia;

d = 0.72, 95%CI 0.61 to 0.84, Q_w = 55.78, p = 0.001

Central

Significant, large effect of reduced P300 amplitude in the central brain region of people with schizophrenia;

d = 0.86, 95%CI 0.75 to 0.97, Q_w = 36.66, p = 0.1998

Parietal

Significant, large effect of reduced P300 amplitude in the parietal cortex of people with schizophrenia;

d = 1.00, 95%CI 0.88 to 1.11, Q_w = 55.20, p = 0.0013

Comparisons between regions

The effect size was significantly greater in the parietal cortex than in the frontal cortex;

Q_B = 10.86, p < 0.0005

No significant differences in effect sizes between frontal and central areas;

Q_B = 2.71, p < 0.1

No significant differences in effect sizes between central and parietal areas; $Q_B = 2.74$, $p < 0.1$ <u>Left hemisphere</u> *Significant, large effect of reduced P300 amplitude in the left hemisphere of people with schizophrenia;* 11 studies, N not reported, $d = 0.85$, 95%CI 0.70 to 1.01, $Q_w = 57.85$, $p = 0.0001$ *Significant, medium-sized effect of reduced P300 amplitude in the left temporal T3 region of people with schizophrenia;* $d = 0.79$, 95%CI 0.61 to 0.97, $Q_w = 41.20$, $p = 0.0003$ *Significant, large effect of reduced P300 amplitude in the left temporal TCP1 region of people with schizophrenia;* $d = 1.06$, 95%CI 0.74 to 1.38, $Q_w = 14.48$, $p = 0.07$ <u>Right hemisphere</u> *Significant, medium-sized effect of reduced P300 amplitude in the right hemisphere of people with schizophrenia;* $d = 0.61$, 95%CI 0.46 to 0.76, $Q_w = 41.89$, $p = 0.0093$ *Significant, medium-sized effect of reduced P300 amplitude in the right temporal T4 region of people with schizophrenia;* $d = 0.61$, 95%CI 0.44 to 0.78, $Q_w = 25.28$, $p = 0.0464$ *Significant, medium-sized effect of reduced P300 amplitude in the right temporal TCP2 region of people with schizophrenia;* $d = 0.61$, 95%CI 0.31 to 0.91, $Q_w = 16.62$, $p = 0.0344$ <u>Comparisons between hemispheres</u> *The effect size was significantly greater in the left hemisphere than in the right hemisphere;* $Q_B = 4.93$, $p = 0.03$ *There was no significant difference in effect sizes between T3 and T4;* $Q_B = 1.99$, $p = 0.16$ *There was no significant difference in effect sizes between TCP1 and TCP2;* $Q_B = 1.99$, $p = 0.16$	
Consistency in results	Significant heterogeneity is reported in all lateral and in Pz and Fz categories, as well as between hemispheres and TCP categories, and Pz-Fz category.
Precision in results	Precise for all outcomes.
Directness of results	Direct

Jeon YW, Polich J

Meta-analysis of P300 and schizophrenia: patients, paradigms and practical implications

Psychophysiology 2003; 40(5): 684-701

View review abstract online

Comparison	Comparison of P300 amplitude and latency in people with schizophrenia vs. controls.
Summary of evidence	Moderate quality evidence (small to medium-sized samples, inconsistent precise, direct) suggests P300 amplitude is reduced and P300 latency is increased in people with schizophrenia across a range of tasks. These effects were significantly influenced by many sample, patient and stimulus moderator variables.

P300 activity

Measured as the mean response of parietal and central electrodes

Oddball auditory paradigm

Significant, large effect of reduced amplitude in people with schizophrenia;

N = 135, d = 0.89, 95%CI 0.84 to 0.94, Q_w = 288.5, p = 0.0000

Significant, medium-sized effect of increased latency in people with schizophrenia;

N = 108, d = 0.59, 95%CI 0.54 to 0.65, Q_w = 426.4, p = 0.0000

Oddball visual paradigm

Significant, small effect of reduced amplitude in people with schizophrenia;

N = 21, d = 0.39, 95%CI 0.25 to 0.52, Q_w = 43.7, p = 0.0025

Significant, small to medium-sized effect of increased latency in people with schizophrenia;

N = 14, d = 0.49, 95%CI 0.31 to 0.68, Q_w = 36.4, p = 0.0009

Selective attention paradigm

Significant, small to medium-sized effect of reduced amplitude in people with schizophrenia;

N = 15, d = 0.47, 95%CI 0.30 to 0.64, Q_w = 25.7, p = 0.0413

Significant, small effect of increased latency in people with schizophrenia;

N = 2, d = 0.43, 95%CI -0.04 to 0.90, Q_w = 1.20, p = 0.5502

Other paradigm (e.g. non-oddball, bimodal, somatosensory)

Significant, small effect of reduced amplitude in people with schizophrenia;

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N = 32, d = 0.28, 95%CI 0.16 to 0.40, Q_w = 119.4, p = 0.0000

Significant, small effect of increased latency in people with schizophrenia;

N = 18, d = 0.32, 95%CI 0.16 to 0.48, Q_w = 28.0, p = 0.0618

Overall

Significant, large effect of reduced amplitude in people with schizophrenia;

N = 203, d = 0.74, 95%CI 0.69 to 0.78, Q_w = 602.5, p = 0.0000

Significant, medium-sized effect of increased latency in people with schizophrenia;

N = 142, d = 0.56, 95%CI 0.51 to 0.61, Q_w = 503.4, p = 0.0000

Comparisons between tasks

Significant difference in amplitude effect sizes across tasks;

Q_B = 125.2, p < 0.0000001

Significant difference in latency effect sizes across tasks;

Q_B = 11.4 p < 0.0099908

Moderator analyses

Amplitude moderator variables, all paradigms together

The following moderator variables were associated with significantly reduced P300 amplitude;

Paranoid subtype (p < 0.0001); earlier age of onset (p < 0.0058); percentage of males < 65% (p = 0.0160); high school level of education attained only (p = 0.0130); lower probability of target stimulus (p = 0.006); shorter interstimulus interval (p = 0.0041); shorter tone duration (p = 0.0010); lesser difference between target and standard stimulus (p = 0.0029); lower stimulus intensity (p = 0.0379); counting response modality (p = 0.0343); electrode at Cz location (p < 0.0001); ear reference location (p = 0.0014); high pass filter applied (p = 0.0164); and non-conventional amplitude measure (p < 0.0001)

Percentage of paranoid subtype was significantly correlated to effect size, r = 0.50, p = 0.001; as was sample size, r = -0.21, p = 0.02

No significant difference was reported for disease severity, disease duration, medication status, age, sample size, and target stimulus frequency

Latency moderator variables, all paradigms together

The following moderator variables were associated with increased (delayed) P300 latency;

Paranoid subtype (p < 0.0001); moderate severity (p = 0.0016); acute duration (p < 0.0001); percentage of males < 65% (p < 0.0001); high school level of education attained only (p = 0.0002); younger age (p < 0.0001); larger sample size (p < 0.0001); lower probability of target stimulus (p < 0.0001); shorter interstimulus interval (p = 0.0186); lower stimulus intensity, dB (p < 0.0001); moderate target stimulus frequency Hz (p < 0.0001); electrode at Cz location (p < 0.0001); ear reference location (p < 0.0001); high pass filter applied (p < 0.0001); and non-conventional amplitude measure (p < 0.0001)

Percentage of paranoid subtype was significantly correlated to effect size, r = 0.35, p = 0.04; as was disease duration r = -0.58, p < 0.0001; percentage male r = -0.47, p < 0.0001; education years r = -0.38, p = 0.016; and sample size r = 0.32, p = 0.001

No significant difference was reported for age of onset, medication status, tone duration, and target/standard difference. _Moderator variables for oddball auditory paradigm_ Target probability was significantly correlated to amplitude effect size r = -0.27 p = 0.003 and to latency effect size, r = 0.197 p = 0.048 Stimulus difference was significantly correlated to amplitude effect size r = -0.2245, p = 0.012 and to latency effect size, r = 0.251, p = 0.012 Stimulus intensity was significantly correlated to latency effect size, r = -0.36, p < 0.001, as was target frequency r = 0.28, p = 0.00.6	
Consistency in results	Significant heterogeneity is reported in all outcomes of meta-analysis.
Precision in results	Precise for all outcomes.
Directness of results	Direct

Qiu YQ, Tang YX, Chan RCK, Sun XY, He J. **P300 aberration in first-episode schizophrenia patients: A meta-analysis** **PLoS ONE 2014; 9(6)** View review abstract online	
Comparison	**Comparison of P300 amplitude and latency in people with first-episode schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests a large effect of reduced P300 amplitude, and a medium-sized effect of delayed P300 latency in people with first-episode schizophrenia compared to controls. Inconsistency is explained by differences in task difficulty.**
P300 amplitude	
A large effect of reduced P300 amplitude, and a medium-sized effect of delayed P300 latency in people with first-episode schizophrenia; 17 studies, N = 1316, SMD = -0.83, 95%CI -1.02 to -0.65, p = 0.00001, I² 55%, p = 0.003 16 studies, N = 1213, SMD = 0.48, 95% CI: 0.14 to 0.81, p = 0.005, I² 86%, p < 0.0001 Meta-regression showed that greater task difficulty was associated with higher effect sizes, which	

explained the significant heterogeneity.	
There were no changes in effect size according to sex, age, medication, reaction methods, target ratio or study sites.	
Authors report no evidence of publication bias.	
Consistency in results	Consistent (heterogeneity explained by differences in task difficulty)
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, CZ = central electrode, d = Cohen's d and g = Hedges' g = standardized mean differences (see below for interpretation of effect sizes), EEG = electroencephalogram, ERP = event-related potential, FZ = frontal lobe electrode, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PZ = parietal lobe electrode, Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, Q_B = between group heterogeneity, Q_w = within group heterogeneity, SE = standard error, T3/ TCP1= Left temporal lobe electrodes, SMD = standardised mean difference, T4/TCP2 = Right temporal lobe electrodes, vs. = versus

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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[9].

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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[9].

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[10]. 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

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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. I² 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. I² 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[11].

‖ 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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