# TECHNICAL COMMENTARY

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# Electroencephalography

## Introduction

Electroencephalography (EEG) uses electrodes on the scalp to measure electrical activity from the brain. Quantitative spectral EEG investigates several waveforms, and so the activity can be measured, but EEG also gives rise to event related potentials (ERP), which measure the EEG activity directly evoked by a stimulus, often using cognitive or perceptual stimuli. Error-related negativity is a response-locked ERP that has been associated with monitoring of actions and detecting errors. Error-related negativity is typically followed by the error positivity component. In contrast to error-related negativity and error positivity, feedback negativity is elicited by externally provided feedback about positive rather than negative outcomes.

Spectral waveforms measured by EEG include delta waves (up to 4 Hz), which are slow waves with high amplitude; theta waves (4-7 Hz), which are also slow waves; alpha waves (8-12 Hz), which occur mostly at rest, beta waves (12-30 Hz), which are fast waves with low amplitude, occurring during times of alert concentration, and gamma waves (30-100+ Hz) which occur during certain cognitive and motor functions. One example of an ERP is the P300 wave, which is measured primarily over the parietal lobe and is used as a measure of cognitive function. EEG is also used to measure electrical activity during sleep, to identify disruptions to sleeping patterns.

### 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 were 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 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



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are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

## Results

We found four systematic reviews that met our inclusion criteria[3-6].

- Moderate to high quality evidence finds theta and delta wave activity are increased and P300 amplitude is decreased in people with schizophrenia. Moderate quality evidence also finds increased beta wave activity and decreased alpha wave activity.
- Moderate to high quality evidence finds a large effect of reduced error-related negativity in people with psychosis and a medium-sized effect in those at risk of psychosis. There were no differences in error positivity or feedback negativity.
- Moderate quality evidence finds people with schizophrenia had large effects of shorter total sleep time, more awake time, longer sleep onset latency, and lower sleep efficiency. There were medium-sized effects of increased stage 1 sleep, decreased stage 4 sleep, decreased slow wave sleep, and decreased REM latency. There were small effects of decreased stage 3 sleep and increased REM duration. Moderator analyses found medication-naïve patients had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, and longer awake time. Patients recently withdrawn from antipsychotics had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, longer awake time, increased stage 1 sleep, decreased stage 2, 3, and 4 sleep, decreased slow wave sleep and shorter REM latency. Patients on antipsychotics had significantly longer sleep onset latency, increased stage 2 sleep, and decreased total REM sleep.



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*Boutros NN, Arfken C, Galderisi S, Warrick J, Pratt G, Iacono W*

## The status of spectral EEG abnormality as a diagnostic test for schizophrenia

**Schizophrenia Research 2008; 99(1-3): 225-237**

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| | |
|---|---|
| **Comparison** | **Comparison of the theta, delta, alpha and beta wave activity, measured by spectral EEG in people with schizophrenia vs. controls.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, unable to assess precision and consistency, direct) suggests increased delta, theta, and beta wave activity and decreased alpha wave activity in people with schizophrenia.** |
| **Spectral wave activity** | |
| Total analysis included 15 studies, N = 799<br>Theta θ waves: 13 studies, increased activity, *p* = 00.00000000105<br>Delta δ waves: 13 studies, increased activity, *p* = 0.0000000617<br>Beta $\beta_1$ waves: 6 studies, increased activity, *p* = 0.02<br>Beta $\beta_2$ waves: 8 studies, increased activity, *p* = 0.006<br>Alpha α waves: 7 studies, decreased activity, *p* = 0.001<br>Alpha $\alpha_2$ waves: 7 studies, decreased activity, *p* = 0.0009<br>*Subgroup analysis of unmedicated patients;*<br>Theta θ waves: 7 studies, increased activity, *p* = 0.000069<br>Delta δ waves: 7 studies, increased activity, *p* = 0.00027 | |
| **Consistency in results**‡ | No measure of consistency is reported |
| **Precision in results**§ | No confidence intervals are reported. |
| **Directness of results**‖ | Direct |

*Chan MS, Chung KF, Yung KP, Yeung WF*

## Sleep in schizophrenia: A systematic review and meta-analysis of

## polysomnographic findings in case-control studies

**Sleep Medicine Reviews 2017; 32: 69-84**

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| Comparison | Sleep disturbances in people with schizophrenia vs. controls. |
|---|---|
| Summary of evidence | **Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) finds people with schizophrenia had large effects of shorter total sleep time, more awake time, longer sleep onset latency, and lower sleep efficiency. There were medium-sized effects of increased stage 1 sleep, decreased stage 4 sleep, decreased slow wave sleep, and decreased REM latency. There were small effects of decreased stage 3 sleep and increased REM duration.**<br><br>**Moderator analyses found medication-naïve patients had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, and longer awake time. Patients recently withdrawn from antipsychotics had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, longer awake time, increased stage 1 sleep, decreased stage 2, 3, and 4 sleep, decreased slow wave sleep and shorter REM latency. Patients on antipsychotics had significantly longer sleep onset latency, increased stage 2 sleep, and decreased total REM sleep.** |

**Sleep variables**

*Large, significant effects of;*

Shorter total sleep time: 29 studies, N = 870, $g$ = -0.76, $p < 0.001$, $I^2$ = 81%, $p < 0.001$

More awake time: 17 studies, N = 496, $g$ = 0.80, $p < 0.001$, $I^2$ = 60%, $p < 0.001$

Longer sleep onset latency: 30 studies, N = 913, $g$ = 1.11, $p < 0.001$, $I^2$ = 80%, $p < 0.001$

Lower sleep efficiency: 25 studies, N = 758, $g$ = -0.96, $p < 0.001$, $I^2$ = 76%, $p < 0.001$

*Medium-sized, significant effects of;*

Increased stage 1 sleep: 25 studies, N = 783, $g$ = 0.49, $p < 0.001$, $I^2$ = 70%, $p < 0.001$

Decreased stage 4 sleep: 14 studies, N = 395, $g$ = -0.40, $p < 0.01$, $I^2$ = 43%, $p < 0.05$

Decreased slow wave sleep: 25 studies, N = 784, $g$ = -0.46, $p < 0.001$, $I^2$ = 64%, $p < 0.001$

Decreased REM latency: 28 studies, N = 775, $g$ = -0.40, $p < 0.01$, $I^2$ = 65%, $p < 0.001$

*Small, significant effects of;*

Decreased stage 3 sleep: 14 studies, N = 395, $g$ = -0.25, $p < 0.05$, $I^2$ = 0%, $p > 0.05$

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| Increased REM duration: 17 studies, N = 439, *g* = -0.28, *p* < 0.05, $I^2$ = 29%, *p* > 0.05<br>Moderator analyses found medication-naïve patients had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, and longer awake time. Patients recently withdrawn from antipsychotics had shorter total sleep time, longer sleep onset latency, decreased sleep efficacy, longer awake time, increased stage 1 sleep, decreased stage 2, 3, and 4 sleep, decreased slow wave sleep and shorter REM latency. Patients on antipsychotics had significantly longer sleep onset latency, increased stage 2 sleep, and decreased total REM sleep. REM latency was shorter only in patients with short duration of illness, whereas slow wave sleep and total REM time were reduced in patients with longer duration of illness. |

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| **Consistency in results** | Mostly inconsistent |
| **Precision in results** | Unable to assess; no CIs are reported. |
| **Directness of results** | Direct |

*Galderisi S, Mucci A, Volpe U, Boutros N*

## Evidence-based medicine and electrophysiology in schizophrenia

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

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|---|---|
| **Comparison** | **Comparison of the theta and delta wave activity in people with schizophrenia vs. controls.** |
| **Summary of evidence** | **Moderate to high quality evidence (large samples, precise, mostly inconsistent, direct) suggests theta and delta wave activity are increased, and P300 amplitude is decreased in people with schizophrenia.** |

| **Spectral wave activity** |
|---|
| *Medium effect size suggests increased delta power in people with schizophrenia;*<br>29 studies, N = 2,228, *d* = 0.462, 95%CI 0.345 to 0.578, SE = 0.059, variance = 0.004<br>*Medium effect size suggests increased theta power in people with schizophrenia;*<br>29 studies, N = 2,407, *d* = 0.426, 95%CI 0.328 to 0.524, SE = 0.05, variance = 0.002<br>*Subgroup analysis: medication effects*<br>Stratifying the sample by medication status identified significant between group heterogeneity for theta |

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| band activity, with larger effect sizes for medicated patients<br>Q = 9.45, $p < 0.022$<br>*Subgroup analysis: illness stage (chronic vs. first episode)*<br>Stratifying the sample by illness stage identified significant between group heterogeneity for theta band activity. Chronic patients had larger effect sizes<br>Q = 9.16, $p < 0.01$<br>Stratifying the sample by illness stage identified significant between group heterogeneity for delta band activity. Chronic patients had larger effect sizes<br>Q = 8.89, $p < 0.01$ |
| **P300 amplitude** |
| *Large effect size suggesting reduced P300 amplitude in people with schizophrenia;*<br>52 studies, N = 3,073, $d$ = -0.93, 95%CI -1.034 to -0.821, SE = 0.054, variance = 0.003 |

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|---|---|
| **Consistency in results** | Authors report significant heterogeneity. |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

*Martin EA, McCleery A, Moore MM, Wynn JK, Green MF, Horan WP*

## ERP indices of performance monitoring and feedback processing in psychosis: A meta-analysis

**International Journal of Psychophysiology 2018; Part B. 132: 365-78**

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| | |
|---|---|
| **Comparison** | **ERPs in people with schizophrenia or those at clinical risk vs. controls.** |
| **Summary of evidence** | **Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a large effect of reduced error-related negativity in people with psychosis and a medium-sized effect in those at risk of psychosis. There were no differences in error positivity or feedback negativity.** |
| **Error-related negativity (ERN), error positivity (Pe), and feedback negativity (FN)** | |

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| *A significant, large ERN reduction in people with psychosis;*<br>19 studies, N = 950, *g* = -0.96, 95%CI -1.09 to -0.82, *p* < 0.05, $I^2$ = 50%, *p* = 0.02<br>Subgroup analysis found the effect size from studies that employed non-verbal tasks was larger than the effect size from studies that used verbal tasks (non-verbal *g* = -1.10, verbal *g* = -0.76). There were no differences in effect size according to method of ERN calculation (difference waves vs. error trials), diagnosis (schizophrenia/schizoaffective disorder vs. other psychotic disorders), setting (inpatient vs. outpatient), phase of illness (recent onset vs. chronic), or patient age.<br>*A significant, medium-sized ERN reduction in people at-risk of psychosis;*<br>7 studies, N = 385, *g* = -0.48, 95%CI -0.69 to -0.28, *p* < 0.05, $I^2$ = 43%, *p* = 0.10<br>There were no significant differences in Pe or FN measures. | |
| **Consistency in results** | Inconsistent for patients, consistent for those at risk. |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

## Explanation of acronyms

CI = confidence interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, EEG = electroencephalography, $I^2$ = 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), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, SE = standard error, the percentage of variance not explained by sample error, 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 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[7].

† 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[7].

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[8]. 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.



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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[9].

‖ 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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