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N400 Event related potential

Introduction

The N400 wave is an event-related brain potential (ERP) measured using electroencephalography (EEG). N400 refers to a negativity peaking at about 400 milliseconds after stimulus onset. It has been used to investigate semantic processing, which may be dysfunctional in schizophrenia.

Semantic processing can be separated into two stages; early automatic semantic activation without the involvement of attention, and late contextualisation that is influenced by attention. The semantic priming effect refers to the reduction of reaction time to a word (e.g. table) when it is preceded by a semantically congruent context (e.g. chair) as opposed to a semantically incongruent context (e.g. lake). With a relatively short stimulus onset asynchrony (SOA; less than 500 milliseconds) in word or picture-pair studies, the priming effect is mainly attributed to early automatic semantic activation. With a long SOA (>500 milliseconds), the priming effect is mainly attributed to late contextualisation processes.

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 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 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).

Results

We found one systematic review that met our inclusion criteria[3].

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- High quality evidence shows people with schizophrenia have a medium to large increase in N400 peak latency when compared to controls. They also have a small to medium-sized decrease in N400 amplitude in congruent conditions but not in incongruent conditions. These results are largest in tasks involving long stimulus onset asynchrony. Patients show a decreased N400 semantic priming effect in both short and long stimulus onset asynchrony conditions.

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Wang K, Cheung EFC, Gong Q, Chan RCK

Semantic Processing Disturbance in Patients with Schizophrenia: A Meta-Analysis of the N400 Component

PLoS ONE 2011; 6 (10): e25435

View review abstract online

Comparison	**Comparison of N400 peak latency and amplitude in people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) shows people with schizophrenia have a medium to large increase in N400 peak latency. They also have a small to medium-sized decrease in N400 amplitude in congruent conditions but not in incongruent conditions. These results are largest in tasks involving long stimulus onset asynchrony. Patients show a decreased N400 semantic priming effect in both short and long stimulus onset asynchrony conditions.**

N400 activity

N400 Peak latency

Significant, medium to large effect showing increased N400 peak latency in people with schizophrenia, particularly in long SOA conditions;

All 9 studies: N = 296, d = 0.65, 95%CI 0.36 to 0.95, $p < 0.001$, I^2 = 35.18%, p = 0.13

6 long SOA studies: N = 198, d = 0.82, 95%CI 0.53 to 1.11, $p < 0.001$, I^2 = 0%, p = 0.49

Note: authors state that not enough studies reported short SOA for a separate analysis.

N400 amplitudes for congruent conditions

Significant, small to medium-sized effect showing decreased N400 amplitudes in people with schizophrenia, particularly in long SOA conditions;

All 15 studies: N = 482, d = -0.55, 95%CI -0.92 to -0.19, $p < 0.01$, I^2 = 73.47%, $p < 0.001$

5 short SOA studies: N = 168, d = -0.17, 95%CI -0.52 to 0.17, p = 0.33, I^2 = 50.32%, p = 0.09

7 long SOA studies: N = 212, d = -0.52, 95%CI -0.83 to -0.22, $p < 0.001$, I^2 = 0%, p = 0.56

Note: meta-regression to investigate significant heterogeneity in the all studies analysis reveals that mean daily antipsychotic dosage could partially explain the variance in effect sizes across studies reflecting larger effect sizes for patients with higher dosages (p = 0.01), which authors say may be mediated by symptom severity.

N400 effect (difference in amplitudes between congruent and incongruent conditions)

Significant, medium effect showing a decreased N400 effect in people with schizophrenia in both short

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and long SOA conditions; All 21 studies: N = 740, *d* = -0.64, 95%CI -0.97 to -0.31, *p* < 0.001, I^2 = 77.94%, *p* < 0.001 6 short SOA studies: N = 262, *d* = -0.41, 95%CI -0.66 to -0.17, *p* < 0.001, I^2 = 4.96%, *p* = 0.38 11 long SOA studies: N = 358, *d* = -0.36, 95%CI -0.58 to -0.14, *p* < 0.001, I^2 = 4.73%, *p* = 0.40 Note: meta-regression to investigate significant heterogeneity in the all studies analysis reveals that mean daily antipsychotic dosage could partially explain the variance in effect sizes across studies reflecting larger effect sizes for patients with higher dosages (*p* < 0.05), which authors say may be mediated by symptom severity. <u>N400 Amplitudes for incongruent conditions</u> *No significant differences in N400 amplitudes in incongruent conditions;* All 16 studies: N = 522, *d* = -0.01, 95%CI -0.24 to 0.22, *p* = 0.91, I^2 = 42.64%, *p* = 0.04 5 short SOA studies: N = 164, *d* = -0.24, 95%CI -0.16 to 0.64, *p* = 0.23, I^2 = 53.98%, *p* = 0.07 10 long SOA studies: N = 334, *d* = -0.15, 95%CI -0.43 to 0.13, *p* = 0.30, I^2 = 29.7%, *p* = 0.17 Note: meta-regression to investigate significant heterogeneity in the primary analysis reveals no effect of mean daily antipsychotic dosage (*p* = 0.10).	
Consistency in results‡	Inconsistent for all overall analyses apart from peak latency. Consistent for all subgroup analyses.
Precision in results§	Precise for all except incongruent conditions.
Directness of results‖	Direct

Explanation of acronyms

CI = confidence interval, *d* = standardized mean differences (see below for interpretation of effect sizes), EEG = electroencephalogram, ERP = event-related potential, 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), I^2 = degree of heterogeneity in results across studies, vs. = versus

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[4].

† 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[4].

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[5]. 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. 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[6].

‖ 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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