TECHNICAL COMMENTARY

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Mismatch negativity

Introduction

Mismatch negativity (MMN) is an auditory event-related potential that is generated when a stimulus feature deviates from the regularity of previous auditory stimuli. This deviance can be a simple physical characteristic, such as tone duration, intensity, frequency or location; or more complex abstract presentation characteristics, such as a lower tone in a series of ascending tones. In this way, MMN generation relies on the creation of an auditory (echoic) memory trace for the preceding tones, in order to identify the subsequent deviance. MMN is thought to be an automatic, pre-attentional process and functions as an index of auditory discrimination and echoic memory integrity. MMN is observed as the difference in event-related potential wave response to the standard stimuli and the deviant stimulus. Larger differences between standard and deviant stimuli and lower probability of deviant occurrence are both associated with larger MMN amplitude.

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).

Results

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

- Moderate to high quality evidence finds a large MMN deficit in people with schizophrenia, which was largest in studies

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of chronic patients, in studies using duration deviants rather than frequency or intensity deviants, and when tones were unattended rather than attended.

- Moderate quality evidence finds a medium-sized deficit in duration deviants, but not in pitch deviants, in people with first-episode psychosis.
- Moderate quality evidence finds a medium-sized MMN deficit in people at clinical high risk of schizophrenia, and a small MMN deficit in people at familial high risk of schizophrenia.
- Moderate to low quality evidence finds no associations between MMN deficits and symptom severity.

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Avissar M, Xie S, Vail B, Lopez-Calderon J, Wang Y, Javitt DC

Meta-analysis of mismatch negativity to simple versus complex deviants in schizophrenia

Schizophrenia Research 2018; 191: 25-34

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Comparison	**Comparison of MMN deficits in simple and complex deviant paradigms in people with schizophrenia spectrum disorders vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, precise, direct, unable to assess consistency) suggests medium to large deficits in MMN in both simple and complex paradigm conditions.**
MMN simple or complex deficits	
Medium to large effects of increased deficits in patients; Simple duration: 88 studies, N not reported, SMD = 0.83, 95%CI 0.79 to 0.88, $p < 0.05$ Simple pitch: 64 studies, N not reported, SMD = 0.67, 95%CI 0.59 to 0.75, $p < 0.05$ Simple intensity: 8 studies, N not reported, SMD = 0.60, 95%CI 0.38 to 0.81, $p < 0.05$ Complex abstract/pattern: 5 studies, N not reported, SMD = 0.75, 95%CI 0.45 to 1.05, $p < 0.05$ Complex sensory: 19 studies, N not reported, SMD = 0.59, 95%CI 0.45 to 0.73, $p < 0.05$ Subgroup analysis of duration found a larger effect size in the long than the short duration paradigm (0.92 vs. 0.73). Meta-regression showed a correlation between increased MMN deficits in patients and increased P3b deficit in patients (a subcomponent of P300). The effect size was larger for P3b than for MMN (0.87 vs. 0.65).	
Consistency in results‡	Unable to assess; no measure of consistency is reported.
Precision in results§	Precise
Directness of results‖	Direct

Erickson MA, Ruffle A, Gold JM

A Meta-Analysis of Mismatch Negativity in Schizophrenia: From Clinical Risk to Disease Specificity and Progression

Biological Psychiatry 2016; 79: 980-7

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Comparison 1	**MMN deficits in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) finds a large MMN deficit in people with schizophrenia, which was largest in chronic patients, with tone duration deviants (rather than frequency or intensity), and when tones are unattended.**
MMN deficits	
There was a significant, large effect of MMN deficits in patients vs. controls; 75 samples, N not reported, g = 0.95, 95%CI 0.85 to 1.04, $p < 0.05$ The effect was larger in chronic samples than in first-episode samples (g = 0.81 vs. 0.42). Tone duration deviants produced a larger effect size than tone frequency or tone intensity (g = 0.94 vs. 0.72 vs. 0.62). The effect was larger in paradigms when tones were unattended compared to attended (g = 0.87 vs. 0.59). There was no association between effect size and duration of illness.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	Direct
Comparison 2	**MMN deficits in people at clinical or familial high risk of schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, unable to assess consistency, precise, direct) finds a medium-sized MMN deficit in people at clinical high risk, and a small MMN deficit in people at familial high risk of schizophrenia.**
MMN deficits	
There was a significant, medium-sized MMN deficit in people at clinical high risk, and a trend, small MMN deficit in people at familial high risk; Clinical high risk: 16 samples, N not reported, g = 0.40, 95%CI 0.23 to 0.58, $p < 0.001$ Familial high risk: 8 samples, N not reported, g = 0.26, 95%CI -0.01 to 0.52, p = 0.053 The effect was larger in those at clinical high-risk who developed a psychotic episode by 2-year follow-up compared to those who did not (g = 0.79 vs. 0.17).	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	Direct

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Erickson MA, Albrecht M, Ruffle A, Fleming L, Corlett P, Gold J

No association between symptom severity and MMN impairment in schizophrenia: A meta-analytic approach

Schizophrenia Research: Cognition 2017; 9: 13-7

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Comparison	**Association between MMN deficits and symptom severity in people with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, precise, unable to assess consistency or precision, direct) finds no association between MMN deficits and symptom severity.**
MMN deficits and symptoms	
There were no associations between MMN deficits and symptom severity; Positive symptoms: 62 samples, β = -0.01, *p* = 0.51 Negative symptoms: 68 samples, β = 0.01, *p* = 0.55 There was a significant association between MMN deficits and older age and a trend-level association with lower education.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs reported.
Directness of results	Direct

Haigh SM, Coffman BA, Salisbury DF

Mismatch Negativity in First-Episode Schizophrenia: A Meta-Analysis

Clinical EEG & Neuroscience 2017; 48: 3-10

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Comparison	**Comparison of MMN pitch and duration-deviant paradigms in people with first-episode schizophrenia vs. controls.**

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Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) finds a medium-sized reduction in duration-deviant paradigms, but not pitch-deviant paradigms, in people with first-episode psychosis.**
MMN pitch and duration deviant paradigms	
A significant, medium-sized reduction in duration-deviant paradigms in people with first-episode psychosis; 11 studies, N = 759, d = 0.47, p < 0.05 *There were no significant reductions in pitch-deviant paradigms;* Pitch: 9 studies, N = 572, d = 0.04, p > 0.05 There were no moderating effects of IQ or years of education.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Explanation of acronyms

β = coefficient, CI = confidence interval, d and g = Cohen's d and Hedges' g standardised mean differences, MMN = mismatch negativity, N = number of participants, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant, 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[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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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Avissar M, Xie S, Vail B, Lopez-Calderon J, Wang Y, Javitt DC (2018): Meta-analysis of mismatch negativity to simple versus complex deviants in schizophrenia. *Schizophrenia Research* 191: 25-34.
4. Erickson MA, Albrecht M, Ruffle A, Fleming L, Corlett P, Gold J (2017): No association between symptom severity and MMN impairment in schizophrenia: A meta-analytic approach. *Schizophrenia Research: Cognition* 9: 13-7.
5. Erickson MA, Ruffle A, Gold JM (2016): A Meta-Analysis of Mismatch Negativity in Schizophrenia: From Clinical Risk to Disease Specificity and Progression. *Biological Psychiatry* 79: 980-7.
6. Haigh SM, Coffman BA, Salisbury DF (2017): Mismatch Negativity in First-Episode Schizophrenia: A Meta-Analysis. *Clinical EEG & Neuroscience: Official Journal of the EEG & Clinical Neuroscience Society (ENCS)* 48: 3-10.
7. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
8. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
9. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. Version 3.2 for Windows.