TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Transcranial Magnetic Stimulation

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive method that assesses inhibitory and excitatory mechanisms in the brain.

Inhibitory processes include the cortical silent period, which is measured from the motor evoked potential onset to the return of electromyography. Long and short-interval cortical inhibition involve the pairing of a suprathreshold conditioning stimulus followed by a suprathreshold test stimulus, at either long or short interstimulus intervals.

Excitatory processes include the motor evoked potential amplitude, which is measured as the average response to a series of pulses applied at a consistent TMS intensity. The resting motor threshold is defined as the minimal intensity that produces a motor evoked potential in a relaxed muscle, and intracortical facilitation is a paired-pulse paradigm whereby a conditioning stimulus is applied to the motor cortex before the test stimulus.

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. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. 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.

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 reporting less than 50% of items 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 two systematic reviews that met our inclusion criteria[3, 4].

- High quality evidence suggests decreased motor evoked potential and short-interval cortical inhibition in people with schizophrenia compared to controls. There were no differences in resting motor threshold, intracortical facilitation, cortical silent period, and motor evoked potential amplitude.

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Mehta UM, Thanki MV, Padmanabhan J, Pascual-Leone A, Keshavan MS

Motor cortical plasticity in schizophrenia: A meta-analysis of Transcranial Magnetic Stimulation - Electromyography studies

Schizophrenia Research 2019; 207: 37-47

View review abstract online

Comparison	**Motor evoked potential in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) finds reduced motor evoked potential in people with schizophrenia.**
Motor evoked potential	
Patients demonstrated diminished motor evoked potential; 13 studies, N = 376, d = 0.67, 95%CI 0.49 to 0.86, $p < 0.0001$, Q = 6.46, $p = 0.953$ The results were similar for LTP-like plasticity ($d = 0.66$) and LTD-like plasticity ($d = 0.68$). Heterosynaptic plasticity studies demonstrated a greater effect size ($d = 0.79$) compared to homosynaptic plasticity studies ($d = 0.62$). Clinical, perturbation protocol- and measurement-related factors, and study quality did not moderate the observed effect.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ

A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders

Clinical Neurophysiology 2013; 124(7): 1309-1320

View review abstract online

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Comparison	**Cortical inhibition and excitability in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests decreased short-interval cortical inhibition in people with schizophrenia compared to controls. There were no differences in resting motor threshold, intracortical facilitation, cortical silent period, and motor evoked potential amplitude.**
Short-interval cortical inhibition	
Short-interval cortical inhibition was reduced in schizophrenia; 12 studies, N = 775, g = 0.476, 95%CI 0.331 to 0.620, p = 0.000, I^2 = 1%, p = 0.446	
Resting motor threshold	
No significant differences were found in resting motor threshold; 21 studies, N = 1117, g = 0.067, 95%CI -0.053 to 0.186, p = 0.274, I^2 = 64%, p < 0.001	
Intracortical facilitation	
No significant differences between groups; 11 studies, N = 751, g = 0.015, 95%CI -0.130 to 0.160, p = 0.841, I^2 = 0%, p = 0.507	
Cortical silent period	
No significant differences between groups; 11 studies, N = 791, g = -0.093, 95%CI -0.241 to 0.055, p = 0.218, I^2 = 89%, p < 0.001	
Motor evoked potential amplitude	
No significant differences between groups; 4 studies, N = 184, g = -0.102, 95%CI -0.391 to 0.187, p = 0.489, I^2 = 75%, p = 0.007	
Consistency in results	Consistent for short-interval cortical inhibition and intracortical facilitation only.
Precision in results	Precise
Directness of results	Direct

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Explanation of acronyms

CI = Confidence Interval, *d* and *g* = Cohens d and Hedges' *g* = standardised mean differences, 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 = test for heterogeneity, 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[5].

† 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) that 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[5].

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[6]. 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

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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.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which 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[7].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was comparethat 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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