TECHNICAL COMMENTARY

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Temperature regulation

Introduction

Changes in the homeostatic regulation of body temperature can involve; increased or decreased body temperature in a neutral environment (baseline temperature); altered response to a temperature stimulus (heat or cold stress); changes to the normal differences between morning and nighttime body temperatures (diurnal and circadian variation); variations in the range of typical body temperature changes during the day; and changes to typical differences between core and peripheral body temperatures. At an extreme, temperature dysregulation may be associated with Neuroleptic Malignant Syndrome which can be a side effect of antipsychotic medication. Temperature dysregulation has also been examined in the context of the syndrome of schizophrenia itself.

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.

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 were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. 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 one systematic review that met our inclusion criteria[3].

- In antipsychotic free patients, moderate to low quality evidence suggests baseline temperature may be reduced, there may be less diurnal variation and changes to

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circadian peaks, there may be differences in variation between peripheral and core temperature and an altered response (either greater or less) to temperature stress when compared to controls.

- In mixed groups of antipsychotic free and medicated patients, moderate to low quality evidence suggests baseline temperature may be increased, circadian rhythms may be altered and there may be increased skin temperature following heat stress stimulus when compared to controls.

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Temperature regulation

Chong TW, Castle DJ

Layer upon layer: thermoregulation in schizophrenia

Schizophrenia Research 2004; 69(2-3): 149-157

View review abstract online

Comparison 1	**Comparison of temperature regulation in antipsychotic-free patients vs. healthy controls.** **Note; all studies were performed prior to the introduction of antipsychotic medication.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess precision and consistency, direct) suggests baseline temperature may be reduced, there may be less diurnal variation and changes to circadian peaks, less differences in variation between peripheral and core temperature, and an altered response to temperature stress in people with schizophrenia.**
Baseline temperature in a neutral environment	
3 studies, N = 190 2 studies showed reduced baseline body temperature in patients compared to controls. 1 study found no significant differences between patients and controls, but that the control group's skin temperature increased more than the patients' in the neutral environment.	
Diurnal variation	
1 study, N = 50 reported less diurnal variation in patients, and desynchrony in circadian peaks compared to controls. A longer duration of illness correlated with less temperature dysregulation.	
Differentiation between peripheral and core temperature	
3 studies, N = 166 2 studies showed patients to have a wider temperature differential than controls. 1 study found the temperature differential was wider in controls than patients.	
Heat stress	

Temperature regulation

5 studies, N = 168 1/2 reported patients had a greater increase in skin temperature following stress administration. 1/2 reported controls had a greater increase in skin temperature following stress administration. The remaining 3 studies showed no difference in response.	
Cold stress	
3 studies, N = 160 2 studies reported a difference in cold stress response, with patients showing greater reductions in skin temperature following stress administration. 1 study showed patients have less reduction in skin temperature following stress administration.	
Consistency in results‡	No measure of consistency is reported, although results appear inconsistent.
Precision in results§	No measure of precision is reported.
Directness of results‖	Direct
Comparison 2	**Comparison of temperature regulation in patients vs. healthy controls.** **Note; all studies performed after the introduction of antipsychotic medication (post-1955), but samples vary according to medication status.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess precision and consistency, direct) suggests baseline temperature may be increased, circadian rhythms may be altered, and there may be increased skin temperature following heat stress stimuli in people with schizophrenia.**
Baseline temperature in a neutral environment	
7 studies, N = 347 5 studies showed increased baseline body temperature in patients compared to controls. 1 study found no difference, 1 study found baseline was increased in controls.	
Circadian rhythms	

Temperature regulation

4 studies, N = 395 3 studies showed altered circadian rhythms, with an earlier peak than controls. 1 study showed no difference.	
Heat stress	
3 studies, N = 82 1 study showed patients on antipsychotic treatment had lower initial temperature and a faster rate of skin temperature increase with the application of heat stress stimuli. 2 studies showed untreated patients had higher initial temperature, higher stress related temperature, and greater increase in skin temperature.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Explanation of acronyms

N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant)

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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 which 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.

† 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 randomized 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 effect[4].

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.

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).

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, a 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. A 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

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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.

‡ Inconsistency refers to differing estimates of treatment effect across trials (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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