TECHNICAL COMMENTARY

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Brain weight

Introduction

Brain weight refers to the basic mass measurement of a post-mortem brain, either at time of autopsy ('fresh') or after formalin fixation ('fixed'). Its ease of collection means it is a routine measurement at autopsy and has become a widely used tool for insight into brain integrity. If brain weight is altered, this provides a non-specific indication of neuropathology. It is often a presumed equivalent of the MRI finding of decreased brain volume; see MRI topic for brain volume reviews.

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

- Moderate quality evidence suggests the brain of a person with schizophrenia is significantly lower in weight than a healthy brain.
- Moderate quality evidence suggests that male brain weight is significantly inversely correlated with age at disease onset, such that an earlier age at onset indicated a heavier brain weight.

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Harrison PJ, Freemantle N, Geddes JR **Meta-analysis of brain weight in schizophrenia** **Schizophrenia Research 2003; 64(1): 25-34** View review abstract online	
Comparison	**Post-mortem comparison of brain weight (both fresh and fixed) in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate quality evidence (large sample, imprecise, direct, unable to assess consistency) suggests the brain of a person with schizophrenia weighs significantly less than a healthy brain.** **Moderate to low quality evidence (small sample) suggests male patients who died by suicide had significantly heavier brains than those who died of natural causes.** **Moderate quality evidence (large sample) suggests male brain weight was significantly inversely correlated with age of disease onset, suggesting an earlier age at onset in association with heavier brain weight.**
Brain weight	
Total N = 1,334 Differences in weight: females Mean difference = -36.13g (equivalent to 3.7% lower in patients), 95% CI -68.60 to -4.06g Differences in weight: males Mean difference = -19.32g (equivalent to 3% lower in patients), 95%CI -49.94 to 8.31g Differences in weight overall: multivariate analysis Controlled for age, sex, and interactions between series and diagnosis, age and sex Mean difference = -24g (equivalent to 2% lower in patients), 95%CI 1 to 47g, p = 0.04 Subgroup analysis of mode of death, with age as a covariate *Male patients who died by suicide had significantly heavier brains than those who died of natural causes;* Suicide: 1,583 ± 137g, N = 10 Natural: 1,376 ± 141g, N = 141 F = 8.48, p = 0.004	

A similar trend was observed in female patients (though not significant); Suicide: 1,343 ± 86g, N = 6 Natural: 1,188 ± 132g, N = 106 F = 3.45, *p* = 0.066 Subgroup analysis of age at disease onset *Brain weight was inversely correlated with age at disease onset (after exclusion of one data group with different onset criterion). Relationship was significant only in males;* Males: Pearson's R = -0.257, *p* = 0.021, N = 80 Females: R = -0.220, *p* = 0.058, N = 75 Subgroup analysis of duration of illness, corrected for age at death *No significant correlations were reported between brain weight and duration of illness;* Males: *r* = 0.158, *p* = 0.132 Females: *r* = 0.110, *p* = 0.309	
Consistency in results‡	No measure of consistency is reported.
Precision in results§	Imprecise
Directness of results‖	Direct

Explanation of acronyms

CI = confidence interval, N = number of participants, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), R/*r* = correlation coefficient, 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[4].

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† 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 within-group difference from 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].

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.

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

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difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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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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. Harrison PJ, Freemantle N, Geddes JR (2003): Meta-analysis of brain weight in schizophrenia. *Schizophrenia Research* 64: 25-34.
4. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
5. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
6. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*

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