TECHNICAL COMMENTARY

Neuronal changes

Introduction

Neurons communicate with other cells via synapses. Most neurons have a cell body, an axon, and dendrites. Usually, axons send out signals and dendrites receive signals across the synapse, although synapses can also connect an axon to another axon or a dendrite to another dendrite. This process is partly electrical and partly chemical and can be excitatory or inhibitory. A group of connected neurons is called a neural circuit, involving sensory, motor, and interneurons.

Studies have shown grey matter reductions in people with schizophrenia, which may involve a loss of neurons and/or changes in synaptic density. This topic presents the results of studies assessing changes in neuronal structure.

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 two systematic reviews that met our inclusion criteria[3, 4].

- Moderate to high quality evidence finds a small to medium-sized effect of decreased density of postsynaptic elements in people with schizophrenia, mainly in cortical regions and in dendritic spine density.

- Moderate to high quality evidence finds a small effect of reduced parvalbumin interneuron density in the pre-frontal cortex of people with schizophrenia.

Berdenis van Berlekom A, Muflihah CH, Snijders GJLJ, MacGillavry HD, Middeldorp J, Hol EM, Kahn RS, de Witte LD

Synapse Pathology in Schizophrenia: A Meta-analysis of Postsynaptic Elements in Postmortem Brain Studies

Schizophrenia Bulletin 2019; 46(2): 374-386

View review abstract online

Comparison	Post-mortem comparison of synaptic pathology in people with schizophrenia vs. healthy controls.
Summary of evidence	Moderate to high quality evidence (large sample, inconsistent, precise, direct) finds a small to medium-sized effect of decreased density of postsynaptic elements in people with schizophrenia, mainly in cortical regions and in dendritic spine density.

Density of postsynaptic elements
A small to medium-sized effect of an overall decrease in density of postsynaptic elements in people with schizophrenia; 31 studies, N = 1,096, g = -0.33, 95%CI -0.60 to -0.05, p = 0.020, I^2 = 78.39% Subgroup analyses showed reduction of postsynaptic elements in cortical (mainly prefrontal cortex and cortical layer 3) but not subcortical tissues. There was specifically a decrease for the outcome measure dendritic spine density. There were no moderating effects of age, sex, postmortem interval, or brain bank.

Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Kaar SJ, Angelescu I, Marques TR, Howes OD

Pre-frontal parvalbumin interneurons in schizophrenia: A meta-analysis of post-mortem studies

---

NeuRA | Neuronal changes

October 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 2

TECHNICAL COMMENTARY

Neuronal changes

Journal of Neural Transmission 2019; 126: 1637-51	
View review abstract online	
Comparison	**Post-mortem pre-frontal parvalbumin interneurons in people with schizophrenia vs. healthy controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized sample, consistent, precise, direct) finds a small effect of reduced parvalbumin interneuron density in the pre-frontal cortex of people with schizophrenia.**
Pre-frontal parvalbumin interneurons Parvalbumin cell density and parvalbumin mRNA levels	
A small effect showed reduced parvalbumin interneuron density in the pre-frontal cortex of people with schizophrenia; 9 studies, N = 274, g = -0.27, 95%CI -0.51 to -0.03, p = 0.03, I^2 = 0% There were no moderating effects of post-mortem interval and year of publication. The effect was lower and non-significant in studies using paraformaldehyde or formalin/paraffin-prepared methodology.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, 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), vs. = versus

NeuRA | Neuronal changes   October 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au   Page 3
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

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 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[5].

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[6]. lnOR stands for logarithmic OR where a lnOR of 0 shows no

NeuRA | Neuronal changes

October 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 4

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. I² 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. I² 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 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.

NeuRA | Neuronal changes

October 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 5

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. Berdenis van Berlekom A, Muflihah CH, Snijders GJLJ, MacGillavry HD, Middeldorp J, Hol EM, *et al.* (2019): Synapse Pathology in Schizophrenia: A Meta-analysis of Postsynaptic Elements in Postmortem Brain Studies. *Schizophrenia Bulletin* 46: 374-86.
4. Kaar SJ, Angelescu I, Marques TR, Howes OD (2019): Pre-frontal parvalbumin interneurons in schizophrenia: A meta-analysis of post-mortem studies. *Journal of Neural Transmission* 126: 1637-51.
5. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
6. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
7. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 6