TECHNICAL COMMENTARY

PET and SPECT

Introduction

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are nuclear-based imaging techniques that utilise radioactive tracers to visualise functional brain activity. The radioisotopes tracers are coupled with a biological molecule such as glucose, which is used during cellular metabolism and can be used to highlight areas with changes in metabolic activity. While SPECT offers more limited spatial and temporal resolution than PET, it is less expensive as it does not require a cyclotron in close proximity.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and comprehensive 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 that describes a preferred way to present a meta-analysis. 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 now 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)[1]. 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[2, 3].

- Moderate to low quality evidence finds increased cerebral glucose metabolism in bipolar disorder in the right precentral gyrus, right supplementary motor area, right rolandic operculum, left anterior cingulate / paracingulate gyri and the left optic radiations. There was decreased cerebral glucose metabolism in bipolar disorder in the middle cerebellar peduncles, left superior temporal gyrus, and left middle temporal gyrus.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Toma S, MacIntosh BJ, Swardfager W, Goldstein BI

Cerebral blood flow in bipolar disorder: A systematic review

Journal of Affective Disorders 2018; 241: 505-13

View online review abstract

Comparison 1	**Cerebral blood flow (volume of blood delivered to brain tissue per minute) in people with bipolar disorder vs. controls.**
Summary of evidence	**Low quality evidence (mostly small samples, unable to assess consistency or precision, direct) is unable to determine differences in cerebral blood flow in people with bipolar disorder.**

Cerebral blood flow at rest

6 studies (overall N = 243) found decreased cerebral blood flow in people with bipolar depression compared to controls in the following brain regions;

Anterior temporal

Left parietal

Left superior temporal

Right parietal

Bilateral occipital

Bilateral anterior superior

Middle frontal

Right anterior cingulate

Left anterior superior temporal

Left angular

Left lingual

Bilateral anterior insular

Left dentate nuclei of the cerebellum

Subgenual prefrontal

1 study (N = 41) found increased cerebral blood flow in people with bipolar depression compared to controls in the following brain regions;

Left precentral

Left precuneus

Left inferior parietal

Left posterior cingulate

Right lingual

Right middle temporal

1 study (N = 24) found lower cerebral blood flow ratio in people with bipolar depression compared to controls in the following brain regions;

Left to right hemispheres

4 studies (N = 136) found no differences between people with bipolar depression and controls.

3 studies (N = 64) found decreased cerebral blood flow in people with bipolar mania compared to controls in the following brain regions;

Left frontal

Left parietal

Left anterior cingulate

Right temporal

Anterior cortical

1 study (N = 60) found no differences between people with bipolar mania and controls.

1 study (N = 26) found decreased cerebral blood flow in people in euthymia compared to controls in the following brain regions;

Temporal

Occipital

Medial

Frontal

Cingulate

1 study (N = 28) found no differences between people in euthymia and controls.

1 study (N = 43) found increased cerebral blood flow in people in various mood states compared to controls in the following brain regions;

Left frontal

Temporal

1 study (N = 51) found increased cerebral blood flow in adolescents in various mood states compared to controls in the following brain regions;

Medial frontal

Middle cingulate

1 study (N = 20) found decreased cerebral blood flow in people in various mood states compared to controls in the following brain regions;

Cerebellum

1 study (N = 42) found no differences between people in various mood states compared to controls.

Cerebral blood flow during cognitive tasks

1 study (N = 46) using a memory task found overall decreased cerebral blood flow in people with bipolar disorder compared to controls. *1 study (N = 27) using a reaction time task found increased cerebral blood flow in people with bipolar disorder compared to controls in the following brain regions;* Prefrontal *The same study found decreased cerebral blood flow in people with bipolar disorder in the following brain regions;* Limbic Parietal Premotor *1 study (N = 16) using a verbal learning task found decreased task-related cerebral blood flow response in people with bipolar disorder in the following brain regions;* Dorsolateral prefrontal *1 study (N = 16) using a gambling-type task found increased cerebral blood flow in people with bipolar mania in the following brain regions;* Dorsal anterior cingulate *The same study found decreased cerebral blood flow in people with bipolar mania in the following brain regions;* Left frontal 1 study (N = 64) using a Stroop-type task found no differences in cerebral blood flow. 1 study (N = 16) using a verbal fluency task found no differences in cerebral blood flow. 4 studies found lower cerebral blood flow was associated with poorer task performance on measured tasks of memory, verbal learning, response inhibition, and complex abstraction. In contrast, poor psychomotor performance was related to greater anterior temporal cerebral blood flow and worse performance in a Stroop-type task was associated with greater striatal and temporal cerebral blood flow.	
Comparison 2	**Cerebral blood flow in people with bipolar disorder vs. unipolar depression.**
Summary of evidence	**Low quality evidence (mostly small samples, unable to assess consistency or precision, direct) is unable to determine differences in cerebral blood flow.**
Cerebral blood flow	
2 studies (N = 70) found increased cerebral blood flow in people with bipolar disorder in the following brain regions; Left frontal *1 study (N = 40) found decreased cerebral blood flow in people with bipolar disorder compared to*	

controls in the following brain regions; Left fronto-temporal *The same found increased cerebral blood flow in unipolar depression compared to controls in the following brain regions;* Bilateral anterior temporal Frontal regions *1 study (N = 61) found increased cerebral blood flow in people with bipolar disorder compared to controls in the following brain regions which was not found in people with unipolar depression;* Left prefrontal *1 study (N = 16) using a decision making task found cerebral blood flow differences (region not specified) in people with bipolar mania, which was not found in people with unipolar depression.* *1 study (N = 36 women) using pattern recognition analysis of anterior cingulate regions found cerebral blood flow differentiated bipolar from unipolar depression with 81% accuracy.* 8 studies (N = 210) found no differences in cerebral blood flow between people with bipolar or unipolar depression.	
Consistency in results‡	Unable to assess; no measure of consistency is reported. Appears inconsistent.
Precision in results§	Unable to assess; no measure of precision is reported (CIs).
Directness of results‖	Direct

Wu C, Ren C, Teng Z, Li S, Silva F, Wu H, Chen J

Cerebral glucose metabolism in bipolar disorder: A voxel-based meta-analysis of positron emission tomography studies

Brain and Behaviour 2021; 11(5): e02117

View online review abstract

Comparison	**Cerebral glucose metabolism in people with bipolar disorder vs. controls.**

Summary of evidence	**Moderate to low quality evidence (small to medium sized sample, unable to assess consistency or precision, direct) finds increased cerebral glucose metabolism in bipolar disorder in the right precentral gyrus, right supplementary motor area, right rolandic operculum, left anterior cingulate / paracingulate gyri and the left optic radiations. There was decreased cerebral glucose metabolism in bipolar disorder in the middle cerebellar peduncles, left superior temporal gyrus, and left middle temporal gyrus.**
Cerebral glucose metabolism	
7 studies, N = 286 *The following areas showed increased cerebral glucose metabolism in bipolar disorder;* Right precentral gyrus (BA 6): 220 voxels, MNI = 16, -20, 72, *p* = 0.001 Right supplementary motor area (BA 6): 57 voxels, MNI = 4, -18, 56, *p* = 0.001 Right rolandic operculum (BA 6): 262 voxels, MNI = 58, 8, 10, *p* = 0.000 Left anterior cingulate / paracingulate gyri (BA 24): 264 voxels, MNI = 2, 36, 14, *p* = 0.001 Left optic radiations: 117 voxels, MNI = -22, -32, 2, *p* = 0.001 *The following areas showed decreased cerebral glucose metabolism in bipolar disorder;* Middle cerebellar peduncles: 2030 voxels, MNI = 18, -50, -32, *p* = 0.000 Left superior temporal gyrus (BA 48): 74 voxels, MNI = -42, -14, -10, *p* = 0.002 Left middle temporal gyrus (BA 21): 67 voxels, MNI = -60, -32, -4, *p* = 0 .003 Meta-regressions showed studies with more females showed increased cerebral glucose metabolism in the right lenticular nucleus, putamen, BA48, and left optic radiations, as well as decreased cerebral glucose metabolism in the right anterior cingulate and paracingulate gyri. Longer illness duration was related to increased cerebral glucose metabolism in the right inferior frontal gyrus, triangular part, BA45, left superior frontal gyrus, dorsolateral, and BA10, and decreased cerebral glucose metabolism in the right inferior network and inferior longitudinal fasciculus.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, MNI = Montreal Neurological Institute, N = number of participants, vs. = versus

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].

---

† Different effect measures are reported by different reviews.

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.

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[4].

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 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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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 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, these 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 that 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 and is therefore 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
2. Wu C, Ren C, Teng Z, Li S, Silva F, Wu H*, et al.* (2021): Cerebral glucose metabolism in bipolar disorder: A voxel-based meta-analysis of positron emission tomography studies. *Brain and Behavior* 11 (5) (no pagination).
3. Toma S, MacIntosh BJ, Swardfager W, Goldstein BI (2018): Cerebral blood flow in bipolar disorder: A systematic review. *Journal of Affective Disorders* 241: 505-13.
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*

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au