TECHNICAL COMMENTARY

Physical anomalies

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BIPOLAR DISORDERS LIBRARY

Introduction

First-degree relatives of people with bipolar disorder may show attenuated signs of the illness, such as physical features commonly identified with the disorder. These may include structural and/or functional anomalies as well as sleep disturbances.

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 five systematic reviews that met our inclusion criteria[2-6].

- Moderate quality evidence suggests relatives of people with bipolar disorder show increased grey matter volume in the right inferior frontal gyrus, the left supramarginal gyrus, and the left superior temporal gyrus compared to controls. Decreased grey matter volume was found in relatives in the right lingual gyrus, the right cerebellum, and the right superior frontal gyrus.
- Across all functioning tasks, relatives showed increased activation in the ventral anterior cingulate, right amygdala, and parahippocampal gyrus, and decreased activation in the right inferior parietal gyrus, left postcentral gyrus, and left superior parietal gyrus. During cognitive tasks, relatives showed increased activation in the frontal lobe, right caudate, right inferior frontal gyrus, dorsal anterior cingulate, and left middle temporal gyrus/superior temporal

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gyrus and decreased activation in the parietal lobe. During emotion processing, relatives showed increased activation in the right amygdala, right parahippocampal gyrus, and right middle occipital gyrus. During reward processing, relatives showed increased activation in the anterior and medio-orbital parts of the prefrontal cortex.

- Moderate quality evidence finds decreases in white matter integrity in relatives of people with bipolar disorder in the right corpus callosum body, left corpus callosum splenium, and the left corticospinal tract.
- Moderate quality evidence suggests a medium-sized effect of lower relative amplitude of the sleep-wake cycle in people with bipolar disorder than in people at risk.
- Moderate quality evidence shows a large increase in the P50 ratio in relatives of people with bipolar disorder compared to controls. Increased P50 ratio is measured with EEG and is indicative of reduced cortical inhibition.

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Atagun MI, Drukker M, Hall MH, Altun IK, Tatli SZ, Guloksuz S, van Os J, van Amelsvoort T

Meta-analysis of auditory P50 sensory gating in schizophrenia and bipolar disorder

Psychiatry Research - Neuroimaging 2020; 300: 111078

View online review abstract

Comparison	**P50 ratio in relatives of people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) shows a large increase in the P50 ratio in relatives of people with bipolar disorder.**
P50 ratio	
A large effect of increased P50 S2/S1 ratio in relatives of people with bipolar disorder; 112 studies, N = 5,010, *d* = 2.25, 95%CI 1.74 to 26.06, *p* = 0.02	
Consistency in results‡	Authors report data are inconsistent
Precision in results§	Imprecise
Directness of results‖	Direct

Cattarinussi G, Di Giorgio A, Wolf RC, Balestrieri M, Sambataro F

Neural signatures of the risk for bipolar disorder: A meta-analysis of structural and functional neuroimaging studies

Bipolar Disorders 2019; 21: 215-27

View online review abstract

Comparison	**Brain structure and function in relatives of people with bipolar disorder vs. controls.**

Summary of evidence	**Moderate quality evidence (large samples, some inconsistency, unable to assess precision, direct) suggests relatives of people with bipolar disorder show increased grey matter volume in the right inferior frontal gyrus and left superior temporal gyrus. Decreased grey matter volume was found in relatives in the right lingual gyrus.** **Across all functioning tasks, relatives showed increased activation in the ventral anterior cingulate, right amygdala, and parahippocampal gyrus and decreased activation in the right inferior parietal gyrus, left postcentral gyrus, and left superior parietal gyrus. During cognitive tasks, relatives showed increased activation in the frontal lobe, right caudate, right inferior frontal gyrus, dorsal anterior cingulate, and left middle temporal gyrus/superior temporal gyrus and decreased activation in the parietal lobe. During emotion processing, relatives showed increased activation in the right amygdala, right parahippocampal gyrus, and right middle occipital gyrus. During reward processing, relatives showed increased activation in the anterior and medio-orbital parts of the prefrontal cortex.**

Function

29 studies, N = 79

Across all tasks

Relatives showed increased activation in;

The ventral anterior cingulate (including subgenual and perigenual regions), right amygdala, and parahippocampal gyrus

Relatives showed decreased activation in;

The right inferior parietal gyrus, left postcentral gyrus, and left superior parietal gyrus

Subgroup analysis of child and adult samples found adult relatives showed increased activation in the ventral caudate bilaterally, the left superior temporal gyrus, and the right inferior frontal gyrus, while child relatives showed increased activation in the right parahippocampal gyrus and the right superior temporal gyrus.

During cognitive tasks

Relatives showed increased activation in;

The frontal lobe, right caudate, right inferior frontal gyrus, dorsal anterior cingulate, and left middle temporal gyrus/superior temporal gyrus

Relatives showed decreased activation in;

The parietal lobe

During emotion processing

Relatives showed increased activation in;

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The right amygdala, right parahippocampal gyrus, and right middle occipital gyrus During reward processing *Relatives showed increased activation in;* The anterior and medio-orbital parts of the prefrontal cortex
Structure
13 studies, N = 509 *Increased grey matter volume was found in relatives in;* The right inferior frontal gyrus and left superior temporal gyrus *Decreased grey matter volume was found in relatives in;* The right lingual gyrus Subgroup analysis of child and adult samples found adult relatives showed increased volume in the right inferior frontal gyrus, left superior temporal gyrus and the left cerebellum, while child relatives showed increased volume in the left parahippocampal gyrus and decreased volume in the right cerebellum, right superior temporal gyrus and in the middle frontal gyrus.

Consistency in results	Authors report some analyses were inconsistent.
Precision in results	Unable to assess; no CIs reported.
Directness of results	Direct

Hu R, Stavish C, Leibenluft E, Linke JO

White Matter Microstructure in Individuals With and At Risk for Bipolar Disorder: Evidence for an Endophenotype From a Voxel-Based Meta-analysis

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2020; 5: 1104-13

View online review abstract

Comparison 2	**White matter integrity in relatives of people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) finds decreases in fractional anisotropy in relatives in the right corpus callosum body, left corpus callosum splenium, and left corticospinal tract.**
White matter integrity	

10 studies, N = 753 *Significant decreases in fractional anisotropy in relatives were found in;* Right corpus callosum body: 80 voxels, MNI = 26, 256, 24, $p < 0.00001$ Left corpus callosum splenium: 52 voxels, MNI = 212, 232, 26, $p < 0.00024$ Left corticospinal tract: 37 voxels, MNI = 224, 220, 34, $p = 0.00047$	
Consistency in results	Authors report data were inconsistent.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Ng TH, Chung KF, Ho FY, Yeung WF, Yung KP, Lam TH

Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: a systematic review and meta-analysis

Sleep Medicine Reviews 2015; 20: 46-58

View online review abstract

Comparison	**Sleep efficacy in people at high risk of bipolar disorder (family history and questionnaire scores) vs. people with bipolar disorder in the euthymic phase.**
Summary of evidence	**Moderate quality evidence (small to medium sample size, consistent, precise, direct) suggests a medium-sized effect of lower relative amplitude of the sleep-wake cycle in people with bipolar disorder than in people at risk.**
Sleep variables	
Significant, medium-sized effect of lower amplitude of the sleep-wake cycle in people with bipolar disorder compared to relatives; 3 studies, N = 174, SMD = -0.43, 95%CI -0.83 to -0.02, $p = 0.04$, $I^2 = 43\%$, $p = 0.17$ There were no significant differences in sleep time, efficacy, latency, or wakefulness.	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Zhang W, Sweeney JA, Yao L, Li S, Zeng J, Xu M, Tallman MJ, Gong Q, DelBello MP, Lui S, Nery FG

Brain structural correlates of familial risk for mental illness: a meta-analysis of voxel-based morphometry studies in relatives of patients with psychotic or mood disorders

Neuropsychopharmacology 2020; 45(8): 1369-79

View review abstract online

Comparison	**Grey matter volume in relatives of people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests relatives of people with bipolar disorder may show increased grey matter volume in the right inferior frontal gyrus, the left supramarginal gyrus, and the right rectus gyrus. They may also show decreased grey matter volume in the right cerebellum, and the right superior frontal gyrus.**
Brain structure	
14 studies, N = 1,438 *Relatives showed increased grey matter in;* Right inferior frontal gyrus: 1284 voxels, MNI 42, 22, -4, $p < 0.001$ Left supramarginal gyrus: 724 voxels, MNI -54, -44, 24, $p < 0.001$ Right rectus gyrus: 281 voxels, MNI 12, 12, -16, $p = 0.001$ *Relatives showed decreased grey matter in;* Right cerebellum: 1,039 voxels, MNI 4, -62, -12, $p < 0.001$ Right superior frontal gyrus: 278 voxels, MNI 2, 52, -12, $p < 0.001$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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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), MNI = Montreal Neurological Institute, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, 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[7].

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† 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[7].

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[8]. 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

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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[9].

‖ 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.

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