TECHNICAL COMMENTARY

Gut microbiota

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Introduction

Gut microbiota involves a dynamic community of microorganisms that inhabits the human body, and changes in response to intrinsic and extrinsic factors. This community includes bacteria, archaea, microbial eukaryotes, fungi, and viruses, and so it is critical in maintaining healthy physiology, Disruption to it has been shown to have a pivotal role across a range of medical conditions including inflammatory bowel disease, metabolic diseases, cancer, and chronic pulmonary diseases.

Studies are now investigating how the gut microbiota can influence the brain. The mechanisms by which intestinal microorganisms could be linked to emotional and cognitive functions of the brain are not fully understood, but they are thought to include the vagus nerve, gut hormone signaling, the immune system, tryptophanmetabolism, and microbial metabolites such as short-chain fatty acids.

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 three systematic reviews that met our inclusion criteria[2-4].

- High quality evidence finds increased proxy biomarkers of gut dysbiosis (antibodies against bacterial endotoxins and sCD14) in people with bipolar disorders relative to controls. Lower quality evidence finds zonula may also be increased in bipolar disorder.

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There was reduced gut biodiversity in medicated vs. non-medicated patients.

- Moderate to low quality evidence suggests family Ruminococcaceae, genus Faecalibacterium, and species Faecalibacterium prausnitzii may be reduced in bipolar disorder, while genera Bacteroides or Bacteroides-Prevotella group species may be elevated.

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Nguyen TT, Kosciolek T, Eyler LT, Knight R, Jeste DV

Overview and systematic review of studies of microbiome in schizophrenia and bipolar disorder

Journal of Psychiatric Research 2018; 99: 50-61

View online review abstract

Comparison	**Gut microbiota levels in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency or precision, direct) suggests decreased fractional representation of Faecalibacterium when compared to controls, and reduced gut biodiversity in medicated vs. non-medicated patients.**
Gut microbiota	
1 study (N = 179) found decreased fractional representation of Faecalibacterium and an unclassified member from the Ruminococcaceae compared to healthy controls. Decreased Faecalibacterium was associated with poorer physical health, more depressive symptoms, and worse sleep. 1 study (N = 115) found second generation antipsychotics were associated with reduced gut biodiversity, particularly in female patients. They showed increased levels of Lachnospiraceae, while non-treated patients had higher levels of Akkermansia.	
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

Safadi JM, Quinton AMG, Lennox BR, Burnet PWJ, Minichino A

Gut dysbiosis in severe mental illness and chronic fatigue: a novel trans-diagnostic construct? A systematic review and meta-analysis

Molecular Psychiatry 2021; doi: 10.1038/s41380-021-01032-1

View online review abstract

Comparison	**Levels of proxy biomarkers of gut dysbiosis (gut-microbial diversity) in people with bipolar disorder vs. controls**

Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) finds increased proxy biomarkers of gut dysbiosis (antibodies against bacterial endotoxins and sCD14) in people with bipolar disorders. Lower quality evidence (small sample) also finds increased zonula in bipolar disorder.**
Gut dysbiosis	
Medium-sized effects showed the following proxy biomarkers of gut dysbiosis were increased in bipolar disorder; Antibodies against bacterial endotoxins: 2 studies, N = 545, SMD = 0.72, 95%CI 0.54 to 0.90, $p < 0.05$, $I^2 = 0\%$ sCD14: 3 studies, N = 511, SMD = 0.61, 95%CI 0.15 to 1.07, $p < 0.05$, $I^2 = 76\%$ Zonula: 1 study, N = 82, SMD = 0.77, 95%CI 0.32 to 1.22, $p < 0.05$ *There were no differences in alpha-1-antitripsin levels;* A-1-AT: 1 study, N = 33, SMD = -0.12, 95%CI -0.86 to 0.63, $p > 0.05$ Authors report that elevated levels of gut dysbiosis markers positively correlated with severity of symptoms across all mental disorders.	
Consistency in results	Consistent for antibodies against bacterial endotoxins, inconsistent for sCD14, N/A for zonula and A-1-AT (one study for each).
Precision in results	Precise for antibodies against bacterial endotoxins and zonular, Imprecise for sCD14 and A-1-AT.
Directness of results	Direct for the biomarkers.

Sublette ME, Cheung S, Lieberman E, Hu S, Mann JJ, Uhlemann AC, Miller JM

Bipolar disorder and the gut microbiome: A systematic review

Bipolar Disorders 2021; 23(6): 544-564

View online review abstract

Comparison	**Gut microbiota levels in people with bipolar disorder.**

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Gut microbiota

Summary of evidence	**Moderate to low quality evidence (unclear samples, unable to assess consistency or precision, direct) suggests family Ruminococcaceae, genus Faecalibacterium, and species Faecalibacterium prausnitzii were reduced in bipolar disorder relative to controls in three studies but elevated in a fourth.** **Genera Bacteroides or Bacteroides-Prevotella group species were elevated in bipolar disorder in two studies but lower in a third.**
Gut microbiota	
Authors report that the most convergent taxonomic finding was that family Ruminococcaceae, genus Faecalibacterium, and species Faecalibacterium prausnitzii were reduced in bipolar disorder relative to controls in three studies but elevated in a fourth. Additionally, genera Bacteroides or Bacteroides-Prevotella group species were elevated in bipolar disorder in two studies but lower in a third.	
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

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), 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[5].

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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[5].

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 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[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 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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