TECHNICAL COMMENTARY

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BIPOLAR DISORDERS LIBRARY

Functional magnetic resonance imaging

Introduction

With cognitive, sensory, or motor stimulation, specific brain regions are activated, requiring higher energy use and higher levels of blood flow. Functional magnetic resonance imaging (fMRI) measures blood flow to determine activation and deactivation of the specific brain regions associated with particular tasks. fMRI results from people with bipolar disorder are compared to results from people without bipolar disorder or other comparison groups to help pinpoint the areas of the brain that are affected by the disorder.

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 eleven systematic reviews that met our inclusion criteria[2-12].

During any emotion or cognitive task

- Compared to controls, moderate quality evidence suggests decreased activation in adults with bipolar disorder in the inferior frontal gyrus during cognitive and emotion tasks, and during a mania phase. There were also decreases in the lingual gyrus during cognitive tasks and euthymia, and in the putamen during cognitive tasks. There were increases in activation in the medial temporal lobe, putamen, and pallidum during cognitive tasks and in the caudate.
- Compared to age-matched controls, moderate quality evidence suggests decreased activation in children and adolescents with bipolar disorder in the right ventrolateral prefrontal cortex, right

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dorsolateral prefrontal cortex, right superior frontal gyrus, right dorsal cingulate cortex, and right dorsal striatum. There was also increased activation in patients in the right amygdala, right limbic lobe, right parahippocampal gyrus, right medial prefrontal cortex, right subgenual cingulate cortex, right somatosensory association cortex, left ventral striatum, left ventrolateral prefrontal cortex, left cerebellum, and left lentiform nucleus, putamen, and lateral globus pallidus.

- Compared to age-matched controls, moderate to low quality evidence suggests increased activation in children with a parent with bipolar disorder in the right dorsolateral prefrontal cortex, right insula, right inferior parietal lobule, and left cerebellum.
- Compared to children and adolescents with a parent with bipolar disorder, moderate to low quality evidence suggests decreased activation in children or adolescents with bipolar disorder in the right dorsolateral prefrontal cortex, right insula, and left cerebellum.
- Moderate to low quality evidence suggests more hypoactivation in the putamen of people with bipolar disorder compared to controls than in the putamen of people with major depressive disorder, post-traumatic stress disorder, or an anxiety disorder compared to controls. There were similar levels of hypoactivation in the prefrontal/insula and the inferior parietal clusters. There were similar levels of hyperactivation in the left amygdala/parahippocampal gyrus, the left thalamus, and the perigenual/dorsal anterior cingulate cortex.

During facial affect processing tasks

- Compared to controls, moderate quality evidence suggests decreased activation in people with bipolar disorder in the bilateral ventrolateral prefrontal cortex, and increased activation in bilateral parahippocampal gyrus (including the amygdala), left putamen and left pulvinar. With fear-face stimuli, people with bipolar disorder showed decreased activation in bilateral inferior frontal gyri and the left anterior cingulated gyrus, and increased activation in the left parahippocampal gyrus, left putamen, and left pulvinar thalamus. With happy-face stimuli, people with bipolar disorder showed decreased activation in the right anterior cingulated gyrus and increased activation in bilateral caudate and the left parahippocampal gyrus.
- Compared to age-matched controls, moderate to low quality evidence suggests decreased activation in children or adolescents in the left middle occipital gyrus, and the right inferior frontal gyrus, with increased activity in the right amygdala, right parahippocampal gyrus, left inferior frontal gyrus, and left putamen.
- Compared to adults with bipolar disorder, moderate to low quality evidence suggests increased activation in children or adolescents with bipolar disorder in the right amygdala.
- Compared to people with major depression, moderate quality evidence suggests decreased activation in people with bipolar disorder in the dorsal anterior cingulate gyrus, and increased activation in the parahippocampal gyrus (including the amygdala), bilateral ventral anterior cingulate gyri, and left pulvinar.
- Compared to people with schizophrenia moderate quality evidence suggests decreased activation in people with bipolar disorder in bilateral occipital cunei, and increased activation in the left thalamus pulvinar.

During cognitive control tasks (perceived task difficulty and effort)

- Compared to controls, moderate quality evidence suggests decreased activation in people with bipolar disorder in the right inferior frontal gyrus, the right caudate nucleus, the right angular gyrus, the left inferior temporal gyrus, the left inferior frontal gyrus and the left posterior cingulate

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gyrus. There was also increased activation in the left precentral, left superior frontal, and the right superior temporal gyrus of patients.

During executive functioning tasks

- Moderate quality evidence suggests reduced activation in the striatum, supplementary motor area, precentral gyrus, left cerebral hemisphere, and left cerebellum and more activation in the left gyrus rectus and right middle temporal gyrus. During euthymia there was reduced activation in the striatum, left supplementary motor area, and right inferior parietal gyrus, and more activation in the left gyrus rectus, and right middle and superior temporal lobe. People with bipolar I disorder showed hypoactivation in the putamen, insula, amygdala, supplementary motor area, and left caudate nucleus, and hyperactivation the right superior temporal lobe and left superior frontal gyrus.

During response inhibition tasks

- Moderate quality evidence suggests decreased activation in the right inferior frontal gyrus, left lentiform nucleus, left precuneus, and left postcentral gyrus, with no evidence of increased activation. During euthymia, patients showed decreased activation in the striatum, left supplementary motor area, right anterior cingulate cortex, left lentiform nucleus/putamen, right inferior frontal gyrus, left inferior parietal lobule, right inferior parietal lobule, and the left precuneus. Euthymic patients showed increased activation in the left superior temporal gyrus, right middle frontal gyrus, and in rostral parts of the right inferior frontal gyrus. During mania, patients showed decreased activation in the right inferior frontal gyrus, left medial frontal gyrus, and the anterior cingulate cortex, and increased activation in the right insula and bilateral basal ganglia.

During attention tasks

- Compared to age-matched controls, moderate quality evidence suggests decreased activation in children and adolescents with bipolar disorder in the right anterior cingulate cortex, right limbic areas (including the amygdala), right dorsolateral prefrontal cortex, right lentiform nucleus and right globus pallidus. Increased activation was found in the right middle frontal gyrus, left insula, and bilateral ventrolateral prefrontal cortex of patients.

During working memory tasks

- Moderate quality evidence suggests decreased activation in the left precentral gyrus and left cerebellum, and increased activation in the left gyrus rectus, and right middle and superior temporal lobe. People with bipolar disorder in the euthymic state showed hypoactivation in the left precuneus, right inferior occipital gyrus, and dorsolateral prefrontal cortex, and hyperactivation in the left ventromedial prefrontal cortex and right superior temporal gyrus.

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Alustiza I, Radua J, Pla M, Martin R, Ortuno F

Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit

Schizophrenia Research 2017; 188: 21-32

View online review abstract

Comparison	**Brain activation during cognitive control tasks in people with bipolar disorder vs. controls.** **Cognitive control is defined as the level of perceived difficulty of the cognitive task and the subsequent mental effort that an individual applies to achieve the cognitive aim.**
Summary of evidence	**Moderate quality evidence (large sample, some inconsistency, unable to assess precision, direct) suggests there are decreases in activation in patients in the right inferior frontal gyrus (BA 47), the right caudate nucleus, the right angular gyrus (BA 7), the left inferior temporal gyrus (BA 20), the left inferior frontal gyrus (BA 47), and the left posterior cingulate gyrus (BA 30). There were increases in activation in the left precentral (BA 6), left superior frontal (BA 10), and the right superior temporal gyrus (BA 42).**

Brain activity

12 studies, N = 772

Significant, decreased activation in people with bipolar disorder was found in;

Right inferior frontal gyrus (orbital part, BA 47)

Right caudate nucleus

Right angular gyrus (BA 7)

Left inferior temporal gyrus (BA 20)

Left inferior frontal gyrus (orbital part, BA 47)

Left posterior cingulate gyrus (BA 30)

Significant, increased activation in people with bipolar disorder was found in;

Left precentral (BA 6)

Left superior frontal (BA 10)

Right superior temporal (BA 42)

There was no evidence of publication bias.

Consistency in results‡	Authors report that decreased activation in the right inferior frontal gyrus and caudate nucleus were found in all combinations of studies, indicating consistency for those regions.
Precision in results§	Unable to assess; no measure of precision is reported (CIs).
Directness of results‖	Direct

Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET

A quantitative meta-analysis of fMRI studies in bipolar disorder

Bipolar Disorders 2011; 13: 1-15

View online review abstract

Comparison	**Brain activation in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests decreases in activation in the inferior frontal gyrus during cognitive and emotion tasks and during a mania phase in people with bipolar disorder. There were also decreases in the lingual gyrus during cognitive tasks and euthymia, and the putamen during cognitive tasks. There were increases in activation in the medial temporal lobe, putamen, and pallidum during cognitive tasks, and in the caudate during no specific task paradigm.**

Brain activity

50 studies, N = 1,576

Significant, decreased activation in people with bipolar disorder was found in;

Overall

Inferior frontal gyrus

Lingual gyrus

Putamen

During cognitive tasks

Inferior frontal gyrus

Lingual gyrus

Putamen

During emotion tasks

Inferior frontal gyrus During euthymia Lingual gyrus During mania Inferior frontal gyrus *Significant, increased activation in people with bipolar disorder was found in;* Overall Medial temporal lobe (including the parahippocampus, hippocampus and amydala) Putamen Pallidum Caudate During emotion tasks Medial temporal lobe (including the parahippocampus, hippocampus and amydala) Putamen Pallidum	
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

Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O, Hietala J, Lawrie SM, Martinot JL, McIntosh AM, Meisenzahl E, Frangou S

Common and distinct neural correlates of emotional processing in Bipolar Disorder and Major Depressive Disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies

European Neuropsychopharmacology 2012; 22: 100-13

View online review abstract

Comparison 1	**Brain activation during facial affect processing in people with bipolar disorder vs. controls.**

Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests people with bipolar disorder showed decreased activation in bilateral ventrolateral prefrontal cortex within the inferior frontal gyrus (BA47), and increased activation in bilateral parahippocampal gyrus (including the amygdala), left putamen and left pulvinar.** **With fear-face stimuli, people with bipolar disorder showed decreased activation in bilateral inferior frontal gyri (BA47/45) and the left anterior cingulated gyrus (BA32), and increased activation in the left parahippocampal gyrus (BA 28 and 35), left putamen, and left pulvinar thalamus.** **With happy-face stimuli, people with bipolar disorder showed decreased activation in the right anterior cingulated gyrus (BA32) and increased activation in bilateral caudate and left parahippocampal gyrus (BA34).**
Brain activity	
14 studies, N = 379 *Significant, decreased activation in people with bipolar disorder was found in;* Bilateral ventrolateral prefrontal cortex within the inferior frontal gyri (BA47) Subgroup analysis of fear faces found people with bipolar disorder showed *decreased* activation in bilateral inferior frontal gyri (BA47/45), and the left anterior cingulated gyrus (BA32). Subgroup analysis of happy faces found people with bipolar disorder showed *decreased* activation in the right anterior cingulated gyrus (BA32). *Significant increased activation in people with bipolar disorder was found in;* Bilateral parahippocampal gyri (including the amygdala) Left putamen Left pulvinar Subgroup analysis of fear faces found people with bipolar disorder showed *increased* activation in the left parahippocampal gyrus (BA 28 and 35), left putamen, and left pulvinar thalamus. Subgroup analysis of happy faces found people with bipolar disorder showed *increased* activation in bilateral caudate and left parahippocampal gyrus (BA34).	
Comparison 2	**Brain activation during facial affect processing in people with bipolar disorder vs. people with major depression.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests people with bipolar disorder showed decreased activation in the dorsal anterior cingulate gyrus, and increased activation in the parahippocampal gyrus (including the amygdala), bilateral**

	ventral anterior cingulate gyri, and left pulvinar.
Brain activity	
N = 357 *Significant decreased activation in people with bipolar disorder was found in;* Dorsal anterior cingulate gyrus *Significant increased activation in people with bipolar disorder was found in;* Parahippocampal gyrus (including the amygdala) Bilateral ventral anterior cingulate gyri Left pulvinar There were no direct comparisons between bipolar disorder and major depression for fear vs. happy faces.	
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

Delvecchio G, Sugranyes G, Frangou S

Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of functional imaging studies

Psychological Medicine 2013; 43(3): 553-69

View review abstract online

Comparison	**Brain activation during facial affect processing in people with bipolar disorder vs. people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample size, direct, unable to assess precision or consistency) suggests people with bipolar disorder show decreased activation in bilateral occipital cunei and increased activation in the left thalamus pulvinar.**
Facial affect processing	
29 studies, 1,018 *Significant decreased activation in people with bipolar disorder was found in;*	

Bilateral occipital cuneus (BA18) *Significant increased activation in people with bipolar disorder was found in;* Left thalamus pulvinar Differences between the two disorders in amygdala activation were negatively correlated with antipsychotic dose. Age and sex did not contribute to differences between diagnostic groups.	
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

Hajek T, Alda M, Hajek E, Ivanoff J

Functional neuroanatomy of response inhibition in bipolar disorders - Combined voxel based and cognitive performance meta-analysis

Journal of Psychiatric Research 2013; 47: 1955-66

View online review abstract

Comparison	**Brain activation during response inhibition tasks in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests people with bipolar disorder showed decreased activation in the right inferior frontal gyrus (BA47), left basal ganglia (lentiform nucleus), left precuneus (BA7), and left postcentral gyrus (BA40), with no evidence of increased activation.** **During euthymia, patients showed decreased activation in the left lentiform nucleus/putamen, right inferior frontal gyrus (BA 47), left inferior parietal lobule (BA 40), right inferior parietal lobule, (BA 7), and the left precuneus (BA 7), and increased activation in the left superior temporal gyrus (BA 39), right middle frontal gyrus (BA 10), and in rostral parts of the right inferior frontal gyrus (BA 46).** **During mania, patients showed decreased activation in the right inferior frontal gyrus (BA 47), left medial frontal gyrus (BA9), and the anterior cingulate cortex (BA32), and increased activation in the right insula (BA 13) and bilateral basal ganglia.**
Brain activity	

Significant, decreased activation in people with bipolar disorder was found in; Overall 30 studies, N = 1,302 Right inferior frontal gyrus (BA47) Left basal ganglia (lentiform nucleus) Left precuneus (BA7) Left postcentral gyrus (BA40) During euthymia 12 studies, N = 604 Left lentiform nucleus/putamen Right inferior frontal gyrus (BA 47) Left inferior parietal lobule (BA 40) Right inferior parietal lobule, (BA 7) Left precuneus (BA 7) During mania 10 studies, N = 298 Right inferior frontal gyrus (BA 47) Left medial frontal gyrus (BA9) Anterior cingulate cortex (BA32) *Significant, increased activation in people with bipolar disorder was found in;* During euthymia 12 studies, N = 604 Left superior temporal gyrus (BA 39) Right middle frontal gyrus (BA 10) Rostral parts of the right inferior frontal gyrus (BA 46) During mania 10 studies, N = 298 Right insula (BA 13) Bilateral basal ganglia

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

Janiri D, Moser DA, Doucet GE, Luber MJ, Rasgon A, Lee WH, Murrough JW, Sani G, Eickhoff SB, Frangou S

Shared Neural Phenotypes for Mood and Anxiety Disorders: A Meta-analysis of 226 Task-Related Functional Imaging Studies

JAMA Psychiatry 2019; 77(2): 172-179

View online review abstract

Comparison	**Similarities in brain activation during any task performance in people with bipolar disorder vs. major depressive disorder, post-traumatic stress disorder, or an anxiety disorder.**
Summary of evidence	**Moderate to low quality evidence (large sample, unable to assess consistency or precision, indirect) suggests more hypoactivation in the putamen of people with bipolar disorder compared to controls than in the putamen of people with major depressive disorder, post-traumatic stress disorder, or an anxiety disorder. There were similar levels of hypoactivation in the prefrontal/insula and the inferior parietal clusters. There were similar levels of hyperactivation in the left amygdala/parahippocampal gyrus, the left thalamus, and the perigenual/dorsal anterior cingulate cortex.**

Brain activity

226 studies, N = 9,262

More hypoactivation was found in the putamen of people with bipolar disorder vs. controls than;

Major depressive disorder: 72.17% vs. 17.35%, $p = 0.02$

Post-traumatic stress disorder: 72.17% vs. 4.55%, $p = 0.06$

Anxiety disorders: 72.17% vs. 5.93%, $p = 0.03$

Similar levels of hypoactivation were found across all diagnoses (vs. controls) in;

Prefrontal/insula

Inferior parietal clusters

Similar levels of hyperactivation were found across all diagnoses (vs. controls) in;

Left amygdala/parahippocampal gyrus

Left thalamus

Perigenual/dorsal anterior cingulate cortex

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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	Indirect

Lee MS, Anumagalla P, Talluri P, Pavuluri MN

Meta-analyses of developing brain function in high-risk and emerged bipolar disorder

Frontiers in Psychiatry 2014; 5: 141

View online review abstract

Comparison 1	**Brain activation during any emotion or cognitive task in children and adolescents with bipolar disorder (<19 years) vs. age-matched controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests children or adolescents with bipolar disorder showed decreased activation in the right ventrolateral prefrontal cortex, right dorsolateral prefrontal cortex, right superior frontal gyrus, right dorsal cingulate cortex, and right dorsal striatum. There was increased activation in the right right limbic lobe (including the amygdala and parahippocampal gyrus), right medial prefrontal cortex, right subgenual cingulate cortex, right somatosensory association cortex, left ventral striatum, left ventrolateral prefrontal cortex, left cerebellum, and left lentiform nucleus, putamen, and lateral globus pallidus.**

Brain activity

26 studies, N = 947

Significant, decreased activation in children or adolescents with bipolar disorder was found in;

Right ventrolateral prefrontal cortex

Right dorsolateral prefrontal cortex

Right superior frontal gyrus

Right dorsal cingulate cortex

Right dorsal striatum

Significant, increased activation in children or adolescents with bipolar disorder was found in;

Right limbic lobe (including the amygdala and parahippocampal gyrus) Right medial prefrontal cortex Right subgenual cingulate cortex Right somatosensory association cortex Left ventral striatum Left ventrolateral prefrontal cortex Left cerebellum Left lentiform nucleus, putamen, and lateral globus pallidus	
Comparison 2	**Brain activation during any emotion or cognitive task in children and adolescents with a parent with bipolar disorder vs. age-matched controls.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample) suggests children or adolescents with a parent with bipolar disorder showed increased activation in the right dorsolateral prefrontal cortex, right insula, right inferior parietal lobule, and left cerebellum.**
Brain activity	
6 studies, N = 220 *Significant, increased activation in children or adolescents with a parent with bipolar disorder was found in;* Right dorsolateral prefrontal cortex Right insula Right inferior parietal lobule Left cerebellum	
Comparison 3	**Brain activation during any emotion or cognitive task in children and adolescents with bipolar disorder vs. children and adolescents with a parent with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unclear sample) suggests children or adolescents with bipolar disorder showed decreased activation in the right dorsolateral prefrontal cortex, right insula, and left cerebellum.**
Brain activity	
6 studies, N = unclear *Significant, decreased activation in children or adolescents with bipolar disorder was found in;*	

Right dorsolateral prefrontal cortex Right insula Left cerebellum	
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

Lee MS, Anumagalla P, Talluri P, Pavuluri MN

Attentional engagement increases inferior frontal gyrus activity and mutes limbic activity in pediatric bipolar disorder: Meta-analyses of fMRI studies

Progress in Neuropsychopharmacology and Biological Psychiatry 2018; May

View online review abstract

Comparison	**Brain activation during attention tasks in children and adolescents with bipolar disorder vs. age-matched controls.**
Summary of evidence	**Moderate quality evidence (medium to large sample, unable to assess consistency or precision, direct) suggests children or adolescents with bipolar disorder showed decreased activation in the right anterior cingulate cortex, right limbic areas (including the amygdala), right dorsolateral prefrontal cortex, right lentiform nucleus and right globus pallidus. Increased activation in children or adolescents with bipolar disorder was found in the right middle frontal gyrus, left insula, and bilateral ventrolateral prefrontal cortex.**
Brain activity	
10 studies, N = 358 *Significant, decreased activation in children or adolescents with bipolar disorder was found in;* Right anterior cingulate cortex Right limbic areas (including the amygdala) Right dorsolateral prefrontal cortex Right lentiform nucleus Right globus pallidus *Significant, increased activation in children or adolescents with bipolar disorder was found in;*	

Right middle frontal gyrus Left insula Bilateral ventrolateral prefrontal cortex	
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

Sprooten E, Rasgon A, Goodman M, Carlin A, Leibu E, Lee WH, Frangou S

Addressing reverse inference in psychiatric neuroimaging: Meta-analyses of task-related brain activation in common mental disorders

Human Brain Mapping 38: 2017; 1846-64

View online review abstract

Comparison	**Correlations between anomalies in brain activation during any task performance in people with bipolar disorder and people with other psychiatric disorders.**
Summary of evidence	**Moderate to low quality evidence (large sample, unable to assess consistency or precision, indirect) suggests medium to large correlations between the spatial distribution of brain activation anomalies in people with bipolar disorder and people with other psychiatric disorders.**
Brain activity	
537 studies, N = 10,445 *Significant, medium to large correlations between spatial distribution of brain activity anomalies in people with bipolar disorder vs. controls, and people with other psychiatric disorders vs. controls;* Bipolar disorder and schizophrenia: $r = 0.80$, $p < 0.00001$ Bipolar disorder and major depression: $r = 0.79$, $p < 0.00001$ Bipolar disorder and anxiety disorders: $r = 0.76$, $p < 0.00001$ Bipolar disorder and obsessive-compulsive disorder: $r = 0.53$, $p < 0.00001$	
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	Indirect

Tian F, Diao W, Yang X, Wang X, Roberts N, Feng C, Jia Z

Failure of activation of striatum during the performance of executive function tasks in adult patients with bipolar disorder

Psychological medicine 2020; 50(4): 653-655

View online review abstract

Comparison	**Brain activation during executive functioning in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests reduced activation in the striatum, supplementary motor area, precentral gyrus, left cerebral hemisphere, and left cerebellum and more activation in the left gyrus rectus and right middle temporal gyrus of people with bipolar disorder during executive functioning tasks. During euthymia there was reduced activation in the striatum, left supplementary motor area, and right inferior parietal gyrus, and more activation in the left gyrus rectus, and right middle and superior temporal lobe. People with bipolar I disorder showed hypoactivation in the putamen, insula, amygdala, supplementary motor area, and left caudate nucleus, and hyperactivation the right superior temporal lobe and left superior frontal gyrus.** **During working memory tasks, there was reduced activation in the left precentral gyrus, and left cerebellum, and increased activation in the left gyrus rectus, and right middle and superior temporal gyrus. People with bipolar disorder in the euthymic state showed hypoactivation in the left precuneus, right inferior occipital gyrus, and dorsolateral prefrontal cortex, and hyperactivation in the left ventromedial prefrontal cortex and right superior temporal gyrus.** **During inhibition tasks there was reduced activation in the left and right putamen, left supplementary motor area and right inferior frontal gyrus. During euthymia, there was reduced activation in the striatum, left supplementary motor area, and right anterior cingulate cortex.**
Brain activity	
19 studies, N = 947 All tasks	

People with bipolar disorder showed hypoactivation in;

Bilateral striatum

Supplementary motor area

Precentral gyrus

Left cerebral hemisphere

Left cerebellum

People with bipolar disorder showed hyperactivation in;

Left gyrus rectus

Right middle temporal gyrus

People with bipolar disorder in the euthymic state showed hypoactivation in;

Bilateral striatum

Left supplementary motor area

Right inferior parietal gyrus

People with bipolar disorder in the euthymic state showed hyperactivation in;

Left gyrus rectus

Right middle temporal gyrus

Right superior temporal gyrus

People with bipolar disorder I showed hypoactivation in;

Putamen

Insula

Amygdala

Supplementary motor area

Caudate nucleus of the left cerebral hemisphere

People with bipolar disorder I showed hyperactivation in;

Right superior temporal

Left superior frontal gyrus

During working memory tasks

People with bipolar disorder showed hypoactivation in;

Left precentral gyrus

Left cerebellum

People with bipolar disorder showed hyperactivation in;

Left gyrus rectus

Right middle and superior temporal gyrus *People with bipolar disorder in the euthymic state showed hypoactivation in;* Left precuneus Right inferior occipital gyrus Dorsolateral prefrontal cortex *People with bipolar disorder in the euthymic state showed hyperactivation in;* Left ventromedial prefrontal cortex Right superior temporal gyrus During inhibition tasks *People with bipolar disorder showed hypoactivation in;* Left and right putamen Left supplementary motor area Right inferior frontal gyrus *People with bipolar disorder in the euthymic state showed hypoactivation in;* Bilateral striatum Left supplementary motor area Right anterior cingulate cortex

Consistency in results	Authors report some inconsistency.
Precision in results	Unable to assess; no measure of precision is reported (CIs).
Directness of results	Direct

Wegbreit E, Cushman GK, Puzia ME, Weissman AB, Kim KL, Laird AR, Dickstein DP

Developmental meta-analyses of the functional neural correlates of bipolar disorder

JAMA Psychiatry 2014; 71: 926-35

View online review abstract

Comparison 1	**Brain activation during facial affect processing in children and adolescents with bipolar disorder vs. controls.**

Summary of evidence	**Moderate to low quality evidence (unclear sample, unable to assess consistency or precision, direct) suggests decreased activity in left middle occipital gyrus, and right inferior frontal gyrus, and increased activity in the right amygdale, right parahippocampal gyrus, left inferior frontal gyrus, and left putamen of youth with bipolar disorder.**
Brain activity	
6 studies, N = unclear *Significant, decreased activation in children or adolescents with bipolar disorder was found in;* Left middle occipital gyrus Right inferior frontal gyrus *Significant, increased activation in children or adolescents with bipolar disorder was found in;* Right amygdala Right parahippocampal gyrus Left inferior frontal gyrus Left putamen	
Comparison 2	**Brain activation during facial affect processing in adults with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample, unable to assess consistency or precision, direct) suggests decreased activity in the bilateral amygdala, bilateral inferior frontal gyrus, and left pregenual anterior cingulate cortex, and increased activity in the left amygdala, bilateral striatum, and left inferior frontal gyrus of adults with bipolar disorder.**
Brain activity	
24 studies, N = unclear *Significant, decreased activation in adults with bipolar disorder was found in;* Bilateral amygdala Bilateral inferior frontal gyrus Left pregenual anterior cingulate cortex *Significant, increased activation in adults with bipolar disorder was found in;* Left amygdala Bilateral striatum Left inferior frontal gyrus	
Comparison 3	**Brain activation during facial affect processing in children and**

	adolescents with bipolar disorder vs. adults with bipolar disorder.
Summary of evidence	**Moderate to low quality evidence (unclear sample, unable to assess consistency or precision, direct) suggests increased activity in the right amygdala of youth with bipolar disorder.**
Brain activity	
Number of studies is unclear *Significant, increased activation in children or adolescents with bipolar disorder was found in;* Right amygdala	
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, N = number of participants, *p* = probability of obtaining that result ($p < 0.05$ generally regarded as significant), 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[13].

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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[13].

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[14]. 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

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[15].

‖ 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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References

1. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
2. Alustiza I, Radua J, Pla M, Martin R, Ortuno F (2017): Meta-analysis of functional magnetic resonance imaging studies of timing and cognitive control in schizophrenia and bipolar disorder: Evidence of a primary time deficit. *Schizophrenia Research* 188: 21-32.
3. Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET (2011): A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disorders* 13: 1-15.
4. Delvecchio G, Fossati P, Boyer P, Brambilla P, Falkai P, Gruber O*, et al.* (2012): Common and distinct neural correlates of emotional processing in Bipolar Disorder and Major Depressive Disorder: a voxel-based meta-analysis of functional magnetic resonance imaging studies. *European Neuropsychopharmacology* 22: 100-13.
5. Delvecchio G, Sugranyes G, Frangou S (2013): Evidence of diagnostic specificity in the neural correlates of facial affect processing in bipolar disorder and schizophrenia: a meta-analysis of functional imaging studies. *Psychological Medicine* 43: 553-69.
6. Hajek T, Alda M, Hajek E, Ivanoff J (2013): Functional neuroanatomy of response inhibition in bipolar disorders - Combined voxel based and cognitive performance meta-analysis. *Journal of Psychiatric Research* 47: 1955-66.
7. Lee MS, Anumagalla P, Talluri P, Pavuluri MN (2014): Meta-analyses of developing brain function in high-risk and emerged bipolar disorder. *Frontiers in Psychiatry* 5: 141.
8. Lee MS, Anumagalla P, Talluri P, Pavuluri MN (2018): Attentional engagement increases inferior frontal gyrus activity and mutes limbic activity in pediatric bipolar disorder: Meta-analyses of fMRI studies. *Progress in Neuropsychopharmacology and Biological Psychiatry* May.
9. Sprooten E, Rasgon A, Goodman M, Carlin A, Leibu E, Lee WH*, et al.* (2017): Addressing reverse inference in psychiatric neuroimaging: Meta-analyses of task-related brain activation in common mental disorders. *Human Brain Mapping* 38: 1846-64.
10. Wegbreit E, Cushman GK, Puzia ME, Weissman AB, Kim KL, Laird AR*, et al.* (2014): Developmental meta-analyses of the functional neural correlates of bipolar disorder. *JAMA Psychiatry* 71: 926-35.
11. Janiri D, Moser DA, Doucet GE, Luber MJ, Rasgon A, Lee WH*, et al.* (2020): Shared Neural Phenotypes for Mood and Anxiety Disorders: A Meta-analysis of 226 Task-Related Functional Imaging Studies. *JAMA Psychiatry* 77: 172-9.
12. Tian F, Diao W, Yang X, Wang X, Roberts N, Feng C*, et al.* (2020): Failure of activation of striatum during the performance of executive function tasks in adult patients with bipolar disorder. *Psychological medicine* 50: 653-5.
13. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
14. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
15. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*