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Neural correlates of cognitive behavioral therapy-based interventions for bipolar disorder: A scoping review

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ABSTRACT

Cognitive Behavioral Therapy (CBT) is among the gold-standard psychotherapeutic interventions for the treatment of psychiatric disorders, including bipolar disorder (BD). While the clinical response of CBT in patients with BD has been widely investigated, its neural correlates remain poorly explored. Therefore, this scoping review aimed to discuss neuroimaging studies on CBT-based interventions in bipolar populations. Particular attention has been paid to similarities and differences between studies to inform future research.

The literature search was conducted on PubMed, PsycINFO, and Web of Science databases in June 2023, identifying 307 de-duplicated records. Six studies fulfilled the inclusion criteria and were reviewed. All of them analyzed functional brain activity data.

Four studies showed that the clinical response to CBT was associated with changes in the functional activity and/or connectivity of prefrontal and posterior cingulate cortices, temporal parietal junction, amygdala, precuneus, and insula. In two additional studies, a peculiar pattern of baseline activations in the prefrontal cortex, hippocampus, amygdala, and insula predicted post-treatment improvements in depressive symptoms, emotion dysregulation, and psychosocial functioning, although CBT-specific effects were not shown.

These results suggest, at the very preliminary level, the potential of CBT-based interventions in modulating neural activity and connectivity of patients with BD, especially in regions ascribed to emotional processing. Nonetheless, the discrepancies between studies concerning aims, design, sample characteristics, and CBT and fMRI protocols do not allow conclusions to be drawn. Further research using multimodal imaging techniques, better-characterized BD samples, and standardized CBT-based interventions is needed.

1. Background

The theoretical framework of Cognitive Behavioral Therapy (CBT) assumes the centrality of belief systems in determining patients' psychological well-being (Beck and Alford, 1967; Ellis, 1994). Accordingly, many CBT techniques aim at restructuring automatic thoughts and dysfunctional beliefs (Beck and Alford, 1967; Beck, 1979) or ideas (Ellis, 1994), ultimately leading to the structuring of a more functional and rational belief system, developing new coping strategies and to a significant and persistent reduction of psychological suffering.

Evidence-based guidelines indicate CBT as the gold standard psychotherapeutic intervention for the treatment of psychiatric disorders, including anxiety disorders and depression (Beck, 2005; Butler et al., 2006; David et al., 2018; Malhi et al., 2021).

With respect to bipolar disorder (BD), although pharmacotherapy remains the primary treatment approach, there is growing evidence showing that drugs combined with psychotherapy improve the overall effectiveness of the treatments (Vieta et al., 2009; Valdivieso-Jiménez, 2023). CBT is one of the most used evidence-based psychotherapies for the treatment of bipolar patients (Novick and Swartz, 2019; Miklowitz et al., 2021). While recognizing the neurobiological component of the disorder, CBT assumes that dysfunctional thoughts and behaviors increase the probability of experiencing depressive or manic symptoms. Therefore, CBT sessions are focused on modifying dysfunctional thought patterns (e.g., hyper-positive thinking) and identifying cognitive or behavioral strategies (e.g., communication skills, problem-solving, sleep

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hygiene, medication monitoring, relaxation) useful to maintain healthy lifestyle habits and cope with stress factors (Vieta et al., 2009; Chiang et al., 2017). In BD, the behavioral strategies often dominate over the cognitive ones.

The effectiveness of CBT has been proved by several randomized clinical trials and meta-analyses (Beck, 2005; Chiang et al., 2017; Ekers et al., 2008; Gould et al., 2012; Hofmann et al., 2012; Hofmann and Smits, 2008; Linardon et al., 2017; Tolin, 2010). Specifically, scientific evidence indicates that individual-/group-based CBT, alone or as adjunctive therapy, has mild-to-moderate effectiveness in improving depressive symptoms, mania severity, and psychosocial functioning and lowering relapse rates (Chiang et al., 2017; Valdivieso-Jiménez, 2023). For example, it has been observed that sessions lasting 90–120 min are more effective than shorter sessions (45–90 min) in improving depressive or mania symptoms (Chiang et al., 2017) and that the post-treatment relapse rate is lower in BD-I versus BD-II patients (Chiang et al., 2017). However, a recent network meta-analysis suggests that, if compared with family therapy and psychoeducation, CBT has a more significant impact on depression but comparable efficacy in stabilizing residual manic symptoms and preventing recurrences (Miklowitz et al., 2021).

Most of the available studies focused on the effect of CBT on symptoms' severity and quality of life, while only a few studies investigated the neural correlates of CBT in psychiatric patients (Beauregard, 2014; Brooks and Stein, 2022; Kumari, 2006; Linden, 2006; Porto et al., 2009; Roffman et al., 2005). This contrasts with the advancement of imaging tools and computational analysis techniques that, in recent decades, have proven helpful in detecting morpho-functional brain alterations in patients suffering from various psychiatric disorders (Carter, 2001; Malhi and Lagopoulos, 2008; Pardo et al., 2016). The primary possibility offered by imaging tools in clinical practice lies in identifying biomarkers that might support diagnostic and therapeutic processes.

Bipolar disorder (BD) is a psychiatric disorder whose neurobiological mechanisms are the object of scientific solid interest (Strakowski, 2022) and for which CBT is described as effective (Chiang et al., 2017; Lam et al., 2009; Malhi et al., 2021; Szentagotai and David, 2009; Ye et al., 2016). BD is a multi-systemic and chronic psychiatric condition that affects about 4.8% of the general population (Merikangas et al., 2011), having a multifaceted clinical course involving manic, depressive, and/or mixed episodes (American Psychiatric Association, 2013). These mood swings worsen the quality of life of patients suffering from BD and make the investigation of the disease more problematic (Altman et al., 2006).

There is growing evidence showing that BD is associated with morpho-functional alterations of partially overlapping brain networks including, among others, the Default Mode Network (DMN), the Executive Control Network (ECN), and the Salience Network (SN) (Bassett et al., 2015; Bi et al., 2022; Dosenbach et al., 2007, 2008; Seeley et al., 2007; Syan et al., 2018; Vargas et al., 2013).

The DMN, which is activated during self-directed/referential cognitive processes (e.g., reflective capacity, mind-wandering), includes the dorsomedial prefrontal cortex (PFC), the posterior cingulate cortex (PCC), and the precuneus (Davey et al., 2016; Hiser and Koenigs, 2018). The ECN (often also named the "Inhibitory Control Network") comprises the ventrolateral and dorsolateral PFC and seems to play a key role in the representation and maintenance of goals during motivated behavior, hence supporting the selection of possible behavioral responses. This network is highly activated during attentional and working memory tasks. Lastly, the SN encompasses regions involved in (re)directing attentional resources toward salient stimuli (i.e., insula, inferior parietal lobule, dorsal anterior cingulate cortex).

Structural alterations within these networks have been suggested to affect emotional balance, resulting in emotional-behavioral instability, extreme moods, and swing from one state to another (Bi et al., 2022; Strakowski et al., 2012; Vai et al., 2014, 2019; Wessa and Linke, 2009). Therefore, in the last decades, growing scientific interest has been focused on understanding whether, and to what extent, psychotherapeutic interventions can affect altered brain networks in BD. Specifically, neuroimaging studies have been carried out aimed at exploring the neurobiological basis capable of validating the efficacy of psychotherapy, in particular of CBT (Beauregard, 2014; Brooks and Stein, 2022; Kumari, 2006; Linden, 2006; Porto et al., 2009). For instance, a recent meta-analysis identified neural changes associated with CBT in several psychiatric disorders, including psychosis, cocaine addiction, eating disorders, major depressive disorder, and anxiety disorders (Yuan et al., 2022). The authors selected 13 studies in which patients performed an emotional or cognitive task during functional Magnetic Resonance Imaging (fMRI) before and after CBT. They found that, after CBT, patients showed decreased activation in the left anterior cingulate cortex (ACC) and left middle frontal gyrus during cognitive tasks. The more consistent reductions were found in the DMN, followed by the ECN and SN (Yuan et al., 2022). Yuan and collaborators concluded that CBT may improve patients' cognitive functions by acting on the inter- and intra-functional connectivity between these brain networks (Yuan et al., 2022).

CBT combined with pharmacological treatment has proven effective in reducing clinical symptoms, improving social functioning, and limiting relapses (Colom and Vieta, 2004; Lam et al., 2003; Scott et al., 2001). However, to our knowledge, a paucity of studies so far have investigated the neural underpinnings of CBT in bipolar patients. Therefore, we conducted the present scoping review to summarise and discuss neuroimaging studies that have explored morpho-functional correlates of response to CBT-based interventions in BD. Particularly, in line with recent indications for scoping reviews, the overarching aim of our work is to identify the knowledge gap in the field, report on the types of available evidence, and investigate how research has been conducted (Munn et al., 2018). Particular attention will be paid to similarities and differences between studies regarding sample characteristics, CBT protocols, and MRI techniques to inform future research.

2. Methods

The search was conducted in June 2023 using the PubMed, PsycINFO, and Web of Science databases. The following keywords were used for the search: ("cognitive behavior" OR "cognitive therapy" OR "behavior therapy" OR "CBT" OR "psychological therapy" OR "cognitive behaviour therapy" OR "cognitive behavior therapy" OR "cognitive behavioral therapy" OR "psychotherapy") AND ("MRI" OR "magnetic resonance imaging" OR "fMRI" OR "functional magnetic resonance imaging" OR "PET" OR "positron emission tomography" OR "SPECT" OR "single photon emission computed/tomography" OR "Diffusion weighted imaging" OR "DWI" OR "Diffusion tensor imaging" OR "DTI") AND ("bipolar*" OR "mania" OR "Manic" OR "Affective Psychosis, Bipolar" OR "Bipolar Affective Psychosis" OR "Psychoses, Bipolar Affective" OR "Psychosis, Bipolar Affective").

The inclusion criteria were: (i) original articles published in peer-reviewed journals; (ii) English language; (iii) the use of neuroimaging techniques that examined neural patterns associated with CBT interventions; (iv) the inclusion of patients with BD as ascertained with standardized tools.

To identify the grey literature, non-empirical studies (e.g., qualitative studies, opinions or comments, letters or editorials) were also included, except for literature reviews. No publication year limit was applied to the search. The first selection process (i.e., deduplication and title and abstract screening) was carried out by one researcher (FG). Then, the full-text screening of the eligible articles was conducted independently by two researchers (FG and MGR), and any discrepancy was solved by discussion and consensus. The literature search retrieved 307 de-duplicate records. After title and abstract screening, 295 articles were excluded because they clearly did not meet the inclusion criteria. Twelve articles were full-text screened and six of them were included in the review i.e., Ives-Deliperi et al. (2013), Deckersbach et al. (2018), Ellard et al. (2018), Chou et al. (2022), and Meyer et al. (2023a, b). A flowchart illustrating the study selection process is presented in Fig. 1.

The following information was extracted from the included studies: study characteristics (first author; year of publication); sample characteristics (sample size, sex, age, BD diagnosis and phase of disease); intervention characteristics (treatment group size; treatment type, treatment duration and setting); neuroimaging related variables (imaging method and task delivered); between- and within-group differences in clinical and imaging outcome variables (e.g., depressive symptoms; brain activity and connectivity).

3. Results

3.1. Study synthesis

Sample characteristics are shown in Table 1.

The studies' sample size ranged from 10 to 59 participants per group, while the mean age of the participants ranged from 30.2 to 44.5 years. Overall, there was a balanced gender representation (female = 48.15%) among the groups (Chou et al., 2022; Deckersbach et al., 2018; Ellard et al., 2018; Ives-Deliperi et al., 2013). Two studies employed overlapping samples (Meyer et al., 2023a, 2023b). However, we included both studies as the MRI outcome measures taken into account by the authors were different.

Fifty-four out of 155 patients (≈35%) had a diagnosis of BD type I, with a current depressive episode (Chou et al., 2022; Deckersbach et al., 2018), while the remaining 101 (≈65 %) had BD either type I or II, 19 of whom with a comorbid anxiety disorder (i.e., generalized anxiety disorder or panic disorder or social phobia) (Ellard et al., 2018; Ives-Deliperi et al., 2013; Meyer et al., 2023a, 2023b).

BD patients had low-to-moderate depressive symptoms, as measured by Hamilton's Depression Rating Scale (HDRS), Hospital Anxiety and Depression Scale (HADS), and Quick Inventory of Depressive Symptomatology (QIDS), while, consistently across the studies, patients did not have clinically relevant manic symptoms, as measured by Young Mania Rating Scale (YMRS) (Chou et al., 2022; Deckersbach et al., 2018; Ellard et al., 2018; Ives-Deliperi et al., 2013; Meyer et al., 2023a, 2023b). Notably, key clinical information, including age at the onset of illness, length of illness, number of psychotic episodes, and pharmacological treatments of BD patients, were missing or only partially reported in the included studies.

Lastly, all the included studies explored functional brain activity and/or connectivity using fMRI. Specifically, one study used a Region of Interest (ROI) approach and focused on multiple nodes of the ECN (i.e., bilateral posterior parietal cortex, dorsolateral PFC), the DMN (i.e., PCC, ventromedial PFC) and the SN (i.e., ventrolateral PFC, dorsal ACC) (Ellard et al., 2018); two studies employed both a ROI-based (i.e.; amygdala, insula, ACC, medial PFC) and a whole-brain approach (Meyer et al., 2023a, 2023b), while three studies explored the whole brain (Chou et al., 2022; Deckersbach et al., 2018; Ives-Deliperi et al., 2013).

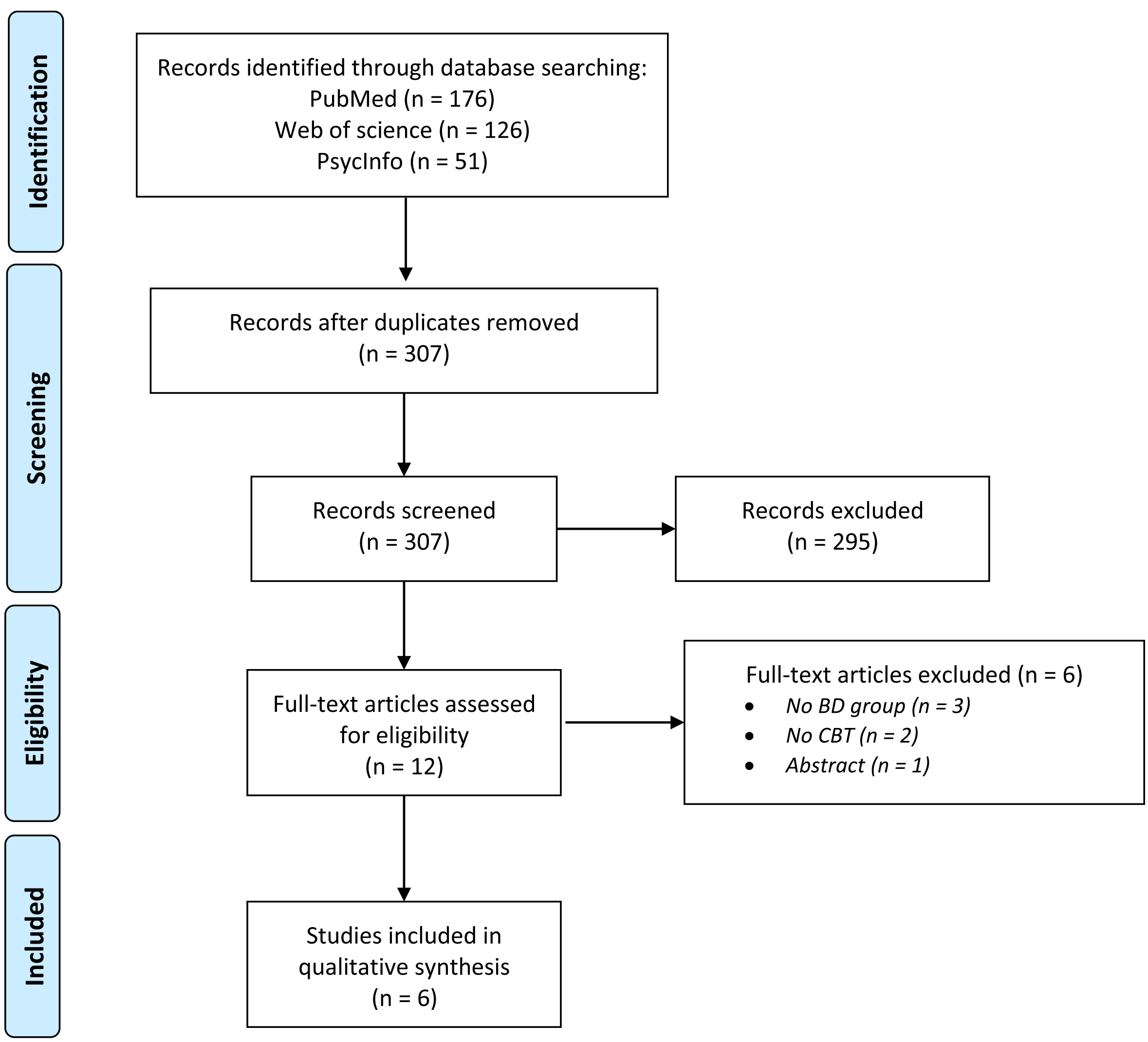

Fig. 1. A flowchart of the articles screening and selection process.

Table 1
Demographic and clinical characteristics of the samples and post-treatment clinical changes in patients with bipolar disorder.

Authors (year)	Sample (M/F)	Age (mean (ds))	Clinical status	Treatment group (size[a])	Interventions' duration and setting	Main results (T1 *vs* T0)
Ives-Deliperi et al. (2013)	23 BD (9/14) 10 HC (2/8)	37.6(9.3) 30.2(5.3)	DSM-IV diagnosis of BD (type I & type II), euthymic state	- MBCT (n = 16) - WL (n = 7)	8 weekly sessions - individual therapy	MBCT - ↑ mindfulness (FFMQ) (p=.01) - ↑ WM (digit span backward) (p=.01) - ↑ visuospatial memory (delayed recall ROCF) (p=.004) - ↑ verbal fluency (COWAT) (p=.02) - ↓ anxiety (BAI) (p=.05) - ↓ emotional dysregulation (DERS) (p=.001)
Chou et al. (2022)	22 BD (14/8) 22 HC (14/8)	37.5 (12.60) 33.32 (8.93)	DSM-IV diagnosis of BD type I, current depressive episode	- MBCT (n = 10) - SP (n = 5)	12 weekly sessions (tot 24 h) – group therapy	MBCT - ↑ mindfulness (FFMQ) (p=.01) SP - no effect
Meyer et al. (2023a) [b]	59 BD (ns) 32 HC (ns)	ns 31.0(8.5)	DSM-5 diagnosis of BD (type I & type II), euthymic state	- SEKT (n = 16) - FEST (n = 17)	4 whole-day sessions in 6 mo (tot 24 h) – group therapy	SEKT and FEST - ↓ symptom severity (LIFE) (p≤ .001) - ↑ global functioning (LIFE) (p≤ .001) - ↑ life satisfaction (LIFE) (p≤ .05)
Meyer et al. (2023b) [b]	59 BD (ns) 32 HC (ns)	ns 30.87 (8.56)	DSM-5 diagnosis of BD (type I & type II), euthymic state	- SEKT (n = 17) - FEST (n = 17)	4 whole-day sessions in 6 mo (tot 24 h) – group therapy	SEKT and FEST - ↓ depression (LIFE) (p≤ .001)
Deckersbach et al. (2018)	32 BD (16/16) 34 HC (19/15)	40.21 (13.13) 33.20 (11.93)	DSM-IV diagnosis of BD type I, current depressive episode	-CBT (n = 17) - SP (n = 15)	18 weekly sessions (tot 15 h) - individual therapy	CBT and SP - ↓ depression (HDRS) (p <.001) - ↑ psychosocial functioning (LIFE-RIFT) (p=.005)
Ellard et al. (2018)	19 BD (10/9)	44.05 (15.42)	DSM-IV diagnosis of BD and anxiety disorders	- TAU (n = 8) - TAU + UP (n = 11)	18 sessions (N hrs) - individual therapy	ns

BAI=Beck Anxiety Index; BD=Bipolar Disorder; CBT=Cognitive Behavioral Therapy; COWAT=Controlled Oral Word Association Test; DERS = Difficulties in Emotion Regulation Scale; DSM-IV/5 = Diagnostic and Statistical Manual of Mental Disorder-Fourth Edition/Fifth Edition; FEST= Fördernde, emotionsfokussierte, supportive Therapie (unstructured emotion-focused intervention); FFMQ=Five-Facet Mindfulness Questionnaire; HC=Healthy Control; HDRS=Hamilton Depression Rating Scale; hrs = hours; LIFE = Longitudinal Interval Follow-Up Evaluation; LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation - Range of Impaired Functioning Tool - Range of Impaired Functioning Tool; M = mean; MBCT = Mindfulness-Based Cognitive Therapy; mo = months; ns = not specified; ROCF=Rey–Osterrieth Complex Figure; SEKT= Spezifische emotional-kognitive Therapie (structured cognitive behavioral intervention); SP=Supportive Psychotherapy; TAU = Treatment As Usual; tot = total; UP=Unified Protocol for Transdiagnostic Treatment of Emotional Disorders; WL=Waiting List.
↑ = increased/stronger/improved; ↓ = decreased/weaker.
[a] number of patients who completed post-treatment evaluations.
[b] overlapping samples.

3.2. Studies design

Four out of the six studies were randomized controlled trials (RCTs). Specifically, BD samples underwent task-related fMRI exams before and after the interventions and were randomized to two experimental conditions, i.e. Mindfulness-Based Cognitive Therapy (MBCT) *versus* Supportive Psychotherapy (SP) (Chou et al., 2022), MBCT *versus* waiting list (Ives-Deliperi et al., 2013) and a structured cognitive behavioral intervention (Spezifische emotional-kognitive Therapie - SEKT) *versus* unstructured emotion-focused intervention (Fördernde, emotions-fokussierte, supportive Therapie - FEST) (Meyer et al., 2023a, 2023b).

In the remaining two studies, patients with BD underwent a resting-state fMRI only before treatment, and the baseline brain functional connectivity patterns were examined to predict baseline and treatment-related changes (Deckersbach et al., 2018; Ellard et al., 2018). In these studies, patients received traditional CBT *versus* SP (Deckersbach et al., 2018) or Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP) *versus* Treatment As Usual (TAU) (Ellard et al., 2018).

3.3. Psychotherapeutic interventions

3.3.1. CBT-based interventions

Regarding individual interventions, Deckersbach et al. (2018) proposed a first-wave CBT protocol, i.e. an adaptation of the Systematic Treatment Enhancement Program (STEP) for bipolar disorder protocol developed by the National Institute of Mental Health (Sachs et al., 2003). The treatment lasted 18 weekly sessions. The first nine were dedicated to psychoeducation, ABC (i.e., antecedents, beliefs, consequences) collection, cognitive restructuring interventions, and activity planning (included a phase focused on the treatment of depressive symptoms); the following seven sessions focused on the treatment of the main areas of illness (i.e., psychiatric comorbidities and emotional regulation). Finally, the last two sessions aimed to prevent the risk of relapse (Deckersbach et al., 2018). Equal in duration was the transdiagnostic CBT protocol (i.e., UP) aimed at improving emotion regulation skills, a process implicated in both anxious and depressive symptomatology (Ellard et al., 2018). Conversely, Ives-Deliperi and colleagues did not detail their 8-session MCBT protocol (Ives-Deliperi et al., 2013).

Concerning group psychotherapy, Chou et al. proposed 12 weekly sessions of MCBT comprising psychoeducation, mood monitoring, identification of relapse risk factors, and initial mindfulness exercises (sessions 1–3); formal practice exercises (i.e., body scans, mindful movement exercises, and breath awareness sitting meditations) accompanied by psychoeducation on BD maintenance factors and problem-solving techniques (sessions 4–7); and teaching self-compassion and emotional self-regulation techniques (sessions 7–12) (Chou et al., 2022). By contrast, the SEKT intervention by Meyer et al. consisted of four whole-day sessions delivered within six months.

Specifically, the protocol combined elements of CBT, MBCT, metacognitive therapy, and interpersonal and social rhythm therapy (Meyer et al., 2023a, 2023b). It included four modules: 1) psychoeducation on BD and mood monitoring with mood/activity diary; 2) identification of early warning signs and improvement of interpersonal skills and problem-solving skills; 3) ABC collection, cognitive restructuring, and metacognitive skills development (e.g., detached mindfulness); 4) self-control skills (e.g., impulse and emotion regulation, reappraisal, and meditation) (Meyer et al., 2023a, 2023b).

Both the MCBT and the SEKT lasted a total of 24 hours.

3.3.2. Control interventions

Four out of six studies included a control intervention. Specifically, two studies included SP, and two used FEST (Chou et al., 2022; Deckersbach et al., 2018; Meyer et al., 2023a, 2023b). These interventions were unstructured and aimed to help patients express their thoughts and emotions and provide them with a sense of support and empathic understanding. In particular, the SP included psychoeducational sessions and exercises such as creating charts reflecting the patients' mood (Chou et al., 2022; Deckersbach et al., 2018). The FEST protocol was emotion-focused and offered psychoeducational elements about BD to patients, but no exercises or homework weren't expected (Meyer et al., 2023a, 2023b).

3.4. fMRI tasks

In the studies by Deckersbach et al. and Ives-Deliperi et al., BD patients and HC were asked to perform respectively a memory or a mindfulness task during fMRI, before (BD and HC) and after (only BD) the interventions (Deckersbach et al., 2018; Ives-Deliperi et al., 2013). Conversely, in the two studies by Meyer et al. BD patients performed an affective Theory of Mind (aToM) (Meyer et al., 2023a) or an emotional face-matching (Meyer et al., 2023b) task during fMRI before and after interventions, while HC participants were scanned twice, by applying the same fMRI protocol and time interval, but without undergoing any treatment.

The mindfulness task consisted of three phases i.e., a first control phase (2 min), an active phase (6 min), and a second control phase (2 min). In the control phases, participants were asked to randomly generate numbers to induce focused attention on a distracting activity. In the active phase, the patients were asked to begin a mindfulness meditation (non-judgmental observation of the breath, bodily sensations, thoughts, and emotions) when the word "meditate" appeared on the screen.

The memory task consisted of a verbal-visual task composed of a fixation block (30 s), four verbal learning blocks (36 s each), and an additional fixation block (30 s) (Deckersbach et al., 2018). Patients were told to rest in the fixation condition while looking at a black fixation cross on a grey screen. In the learning blocks, patients were asked to learn 12 semantically related words (*Directed* condition) and 12 semantically unrelated words (*Unrelated* condition). Only in the *Directed* condition were participants informed that the words could be memorized by grouping them into semantic categories. After the fMRI exam, participants performed free recall and recognition tasks of previously learned words (Deckersbach et al., 2018).

The aToM task was a 480-s cartoon task consisting of 2 conditions presented alternately (Meyer et al., 2023a). In the eight aToM conditions, participants were asked to infer the protagonist's affective mental state and to note whether it was better, worse, or the same as the previous image. The eight control conditions were a working memory task in which participants were asked to count the number of living things in the images and say whether they were more, less, or equal to the previous image. Before scanning, participants underwent a training session outside the scanner to familiarize themselves with the task (Meyer et al., 2023a).

Finally, the emotional face-matching task consisted of 4 blocks of a face-matching task alternated with 5 blocks of a sensorimotor control task (Meyer et al., 2023b). During the face blocks, participants were asked to detect which of the two faces at the bottom of the screen was identical to the target's fearful or angry face at the top. The control blocks resembled the face-matching block, but the faces were replaced with geometric shapes. In both conditions, stimuli were presented for 4 s with a fixed (1.5 s sensorimotor task) or variable (from 1.5 to 5.5 s face-matching task) interstimulus interval (Meyer et al., 2023b).

3.5. Treatment clinical response in BD

Post-treatment clinical changes in patients with bipolar disorder are shown in Table 1.

Two studies indicate that BD patients treated with MCBT showed improvements in anxiety symptoms, emotional regulation capacity, cognitive functioning (verbal working memory, long-term visuospatial memory, vocabulary access) (Ives-Deliperi et al., 2013) and mindfulness skills (i.e., observing, describing, acting with awareness, non-judgment of inner experience, and non-reactivity to inner experience) (Chou et al., 2022; Ives-Deliperi et al., 2013).

Two other research groups found that CBT-based and non-CBT-based interventions were equally effective regarding clinical outcomes. Specifically, BD patients showed a significant reduction of depressive symptoms (Deckersbach et al., 2018; Meyer et al., 2023a, 2023b), global functioning, and life satisfaction (Deckersbach et al., 2018; Meyer et al., 2023a), regardless of the clinical state (current moderate depressive episode or euthymic) and the treatment delivered (i.e., first-wave CBT *versus* SP; SEKT *versus* FEST) (Deckersbach et al., 2018; Meyer et al., 2023a, 2023b).

3.6. fMRI results

3.6.1. Pre-treatment comparison between BD and HC

Looking at the baseline differences between BD and control groups, one research group found that patients with BD had reduced activity in the medial PFC during the mindfulness task (Ives-Deliperi et al., 2013). In addition, a distinct study reported a significant difference in the resting state connectivity between the dorsolateral PFC and the PPC in BD patients and HC. Specifically, the functional activity of these two regions was positively correlated in BD patients and negatively correlated in HC (Chou et al., 2022).

Conversely, the two works by Meyer and colleagues did not reveal baseline differences in the activation of brain regions of their interest (i.e., temporoparietal junction (TPJ), dorsomedial PFC, PCC, and precuneus) during the aToM task (Meyer et al., 2023a), or the face-matching task (i.e., amygdala and other emotion processing-related regions) (Meyer et al., 2023b).

3.6.2. Post-treatment changes in BD

Neuroimaging outcomes from studies investigating post-treatment neurofunctional changes in patients with bipolar disorder are shown in Table 2.

MBCT was associated with changes in brain functional activity in both resting-state and task-related conditions. Specifically, a single study revealed that BD patients treated with the 12-session MBCT showed (post-treatment) restoration of the negatively correlated activity between the dorsolateral PFC and the PCC, similar to the one reported in healthy subjects at baseline. Furthermore, the authors found a trend-level association between a greater ability to 'Act with awareness' (as measured by the Five-Facet Mindfulness Questionnaire - FFMQ) and greater change in the dorsolateral PFC-PCC functional connectivity (Chou et al., 2022). Conversely, no post-treatment brain changes were found in the comparison group (SP) (Chou et al., 2022).

A different study involving BD patients treated with the 8-session MCBT *versus* waiting list showed increased activation in the medial PFC and the PCC during the meditation task. Moreover, the within-

Table 2
Brain imaging results in studies exploring post-treatment neurofunctional changes in patients with bipolar disorder.

Authors (year)	Treatment group (size[a])	Imaging method (task)	Main results	
			T1	T1 vs T0
Ives-Deliperi et al. (2013)	- MBCT (n = 16) - WL (n = 7)	fMRI (mindfulness)	MBCT vs WL - ↑ BOLD signal in the mPFC (p=.001) and in the PCC (p=.005)	MBCT - Positive correlation between signal change in the mPFC and increase in mindfulness skills (p=.016)
Chou et al. (2022)	- MBCT (n = 10) - SP (n = 5)	rs-fMRI		MCBT - Negative correlation of dlPFC-PCC activity (p=.021)[b] - ↑ connectivity dlPFC-PCC correlated with ↑ mindfulness skills ('Act with Awareness' subscale of the FFMQ: p=.056) SP - no effect
Meyer et al. (2023a) [d]	- SEKT (n = 16) - FEST (n = 17)	fMRI (aToM)	SEKT vs FEST - ↑ activity of L TPJ (p=.013), R TPJ (p=.014), PCC (p=.035), precuneus (p=.046), L MTG (p=.006) and dlSFG (p=.022) FEST vs SEKT - no effect	
Meyer et al. (2023b) [d]	- SEKT (n = 17) - FEST (n = 17)	fMRI (emotional face-matching)	FEST vs SEKT - ↑ R amygdala (p=.032) - ↑ connectivity R amygdala-L insula (p=.034) - ↑ R lingual gyrus (p=.003)[c], supplementary motor area (p=.018)[c], L precentral gyrus (p=.021)[c] and R precentral gyrus (p=.026)[c] - ↑ connectivity R amygdala-R insula (p≤.001)[c] - ↑ connectivity R amygdala-LMTG (p=.001)[c] FEST ↑ R amygdala correlated with ↓ depressive symptoms (p=.377)	

aToM = affective Theory of Mind; CBT=Cognitive Behavioral Therapy; FEST= Fördernde, emotionsfokussierte, supportive Therapie (unstructured emotion-focused intervention); FFMQ=Five-Facet Mindfulness Questionnaire; fMRI = functional Magnetic Resonance Imaging; MBCT = Mindfulness-Based Cognitive Therapy; mo = months; MTG = Middle Temporal Gyrus; ns = not specified; PCC = posterior cingulate cortex; PFC = prefrontal cortex; rs = resting state; SEKT= Spezifische emotional-kognitive Therapie (structured cognitive behavioral intervention); SFG=Superior Frontal Gyrus; SP=Supportive Psychotherapy; TPJ = Temporal Parietal Junction; WL=Waiting List.
↑ = increased/stronger/improved; ↓ = decreased/weaker/worsen.
L = left; R = right.
d = dorsal; dl = dorsolateral; m = medial; v = ventral; vl = ventrolateral.
[a] number of patients who completed post-treatment evaluations.
[b] before the treatment the dlPFC-PCC connectivity was positively correlated.
[c] uncorrect.
[d] overlapping samples.

group analysis of the MCBT group revealed a post-treatment positive correlation between the signal change in the PFC and the increase in mindfulness skills (Ives-Deliperi et al., 2013).

Lastly, in the first work by Meyer et al., patients who underwent SEKT *versus* FEST showed post-treatment increased activation in the TPJ, left middle temporal gyrus (MTG), PCC, precuneus, and the dorsolateral superior frontal gyrus (SFG) during the aToM task. Nonetheless, in the SEKT group, the was no association between the brain activity changes and long-term clinical outcomes (Meyer et al., 2023a). Conversely, in the second work of Meyer's research group, patients treated with FEST versus SEKT showed increased post-treatment amygdala activation in the FEST *versus* SEKT group during the face-matching task, as well as increased right amygdala-left insula functional connectivity (Meyer et al., 2023b). Notably, the post-treatment increased amygdala activation only in the FEST group was associated with the reduction of depressive symptoms six months after the intervention (Meyer et al., 2023b).

3.6.3. *Association between pre-treatment brain functional patterns and post-treatment clinical changes in BD*

Table 3 presents the neuroimaging findings from studies investigating the association between baseline fMRI patterns and the clinical response to psychotherapy in patients with BD.

Two studies explored whether pre-treatment brain functional activity (either task-related or at-rest) predicted post-treatment changes in clinical outcome measures (Deckersbach et al., 2018; Ellard et al., 2018). Deckersbach et al. found a positive association between baseline activity in the left dorsolateral PFC and right hippocampus during a verbal memory task and post-treatment improvement of depressive symptoms in BD patients, regardless of the treatment group (i.e., first-wave CBT; SP) (Deckersbach et al., 2018). In addition, Ellard and colleagues found that, although with different lateralization (i.e., left, right, or bilateral) and parcellation (e.g., dorsal, ventral) of the involved regions, baseline weaker and stronger connectivity in resting-state networks, including the anterior insula, the ventrolateral PFC and the amygdala predicted increased perceived affective control in BD patients treated with either TAU or UP + TAU. Notably, similar findings were reported when BD patients were considered a single group, regardless of the treatment (Ellard et al., 2018).

4. Discussion

This scoping review aimed to summarize and discuss neuroimaging studies that explored the neural correlates of CBT-based interventions in BD populations. A total of six studies were retrieved. All of them applied functional neuroimaging.

Four studies were RCT exploring the effect of CBT-based interventions (i.e., MCBT or SEKT) *versus* other therapy (i.e., SP or FEST) or no therapy (i.e., WL) on task-related (Ives-Deliperi et al., 2013; Meyer et al., 2023a, 2023b) or resting-state (Chou et al., 2022) brain activity.

Table 3
Brain imaging results in studies exploring the association between baseline fMRI patterns and clinical response to psychotherapy in patients with bipolar disorder.

Authors (year)	Treatment group (size[a])	Imaging method (task)	Main results
Deckersbach et al. (2018)	- CBT (n = 17) - SP (n = 15)	fMRI (verbal memory)	all BD[b] - ↑ activation in L dlPFC ($p<.01$) and R hippocampus ($p<.001$) predicted ↓ depressive symptoms
Ellard et al. (2018)	- TAU (n = 8) - TAU + UP (n = 11)	rs-fMRI	all BD[b] - ↓ L AI - R vlPFC connectivity predicted ↑ affective control (ACS) (all $p \leq .005$) - ↑ bilateral dAI-bilateral amygdala connectivity predicted - ↑ affective control (ACS) (all $p \leq .001$) TAU + UP - ↓ R dAI - R vlPFC connectivity predicted ↑ affective control (ACS) ($p=.05$) - ↑ R dAI - L amygdala connectivity predicted ↑ affective control (ACS) ($p=.003$) - ↓ L vAI - R vlPFC connectivity predicted ↑ affective control (ACS) ($p=.03$) TAU - ↑ L dAI - bilateral amygdala connectivity predicted ↑ affective control (ACS) ($p=.03$) - ↓ L vAI - R vlPFC connectivity predicted ↑ affective control (ACS) ($p=.01$)

ACS = Affective Control Scale; AI = Anterior Insula; BD=Bipolar Disorder; CBT=Cognitive Behavioral Therapy; fMRI = functional Magnetic Resonance Imaging; PFC = prefrontal cortex; rs = resting state; SP=Supportive Psychotherapy; TAU = Treatment As Usual; UP=Unified Protocol for Transdiagnostic Treatment of Emotional Disorders.
↑ = increased/stronger/improved; ↓ = decreased/weaker.
L = left; R = right.
d = dorsal; dl = dorsolateral; m = medial; v = ventral; vl = ventrolateral.
[a] number of patients who completed post-treatment evaluations.
[b] BD patients with post-treatment data, regardless of the treatment group.

The MBCT investigated, including an 8-week protocol delivered individually (Ives-Deliperi et al., 2013) and a 12-week group program (Chou et al., 2022), led to the improvement of patients' mindfulness skills (and the modulation of functional activity and connectivity of the prefrontal (i.e., medial, dorsolateral) and posterior cingulate cortices. Moreover, patients treated individually also ameliorated anxiety, emotional dysregulation, and cognitive functioning (verbal work memory, long-term visuospatial memory, verbal fluency) (Ives-Deliperi et al., 2013).

Interestingly, Chou and colleagues, who reported a post-treatment restoration of a negatively correlated connectivity between dorsolateral PFC and PCC regions, typically found in healthy subjects, suggested that the switch from a positively to a negatively correlated connectivity between these regions may represent a biomarker of improved flexibility in shifting attention from internal to external stimuli (Buckner et al., 2008; Fox et al., 2005). This, in turn, may represent the mechanism underlying the amelioration of mindfulness skills, clinical symptomatology, and cognitive functioning (Chou et al., 2022). Partially in line with the abovementioned results, Meyer and colleagues found that BD patients treated with SEKT had increased post-treatment activation in the TPJ, PCC, precuneus, and MTG during the aToM task while patients treated with the emotion-focused control therapy (i.e., FEST) had increased amygdala activation during the emotional task as well as and greater amygdala-insula functional connectivity (Meyer et al., 2023a, 2023b). The authors suggested that while the cognitive-based and emotion-focused interventions seemed equally effective at the clinical level, their beneficial effects unfolded by different neural pathways (Meyer et al., 2023a, 2023b). The remaining two studies aimed to explore whether baseline task-related (Deckersbach et al., 2018) or resting-state (Ellard et al., 2018) brain activity predicted the clinical response to psychotherapy (i.e., CBT, TAU, or SP). The authors showed that, regardless of the treatment group, improvements in depression and psychosocial functioning (Deckersbach et al., 2018) and emotion regulation (Ellard et al., 2018) were predicted by a specific pattern of baseline activation in regions ascribed to affective and attentional control, i.e. prefrontal cortices, hippocampus, amygdala, and insula. However, the studies' aim, analysis design (Deckersbach et al., 2018) or limitations (Ellard et al., 2018) precluded the detection of CBT-specific effects.

The findings discussed in the present review are fairly consistent with recent evidence showing the effectiveness of (mindfulness-based) CBT for the treatment of bipolar disorders (Xuan et al., 2020) also in the early phase of the disease (Perlini et al., 2020), and suggests that clinical response to the treatment is associated with brain functional changes (mainly increased activity) in prefrontal, posterior cingulate, insular and amygdala regions, which play a key role in emotion processing and affective control, as well as cognitive flexibility and aToM-related skills (i.e., the ability to understand the feeling of others without adopting others emotions (Walter, 2012)). On the other hand, in some studies, a clear difference between CBT and the comparison therapy was not detectable, either because the BD patients were treated as a single group (Deckersbach et al., 2018) or because the interventions were not compared to each other (Chou et al., 2022). Therefore, the paucity of available studies and the methodological differences between them limit the interpretability of the findings, precluding any generalization on the association between CBT and brain functioning.

First of all, the six studies had different designs and objectives, as three RCTs aimed to explore the neural correlates of clinical response to CBT (Chou et al., 2022; Ives-Deliperi et al., 2013; Meyer et al., 2023a), one RCT focused on the neural correlates of an emotion-focused therapy and used the CBT-based therapy as the control intervention (Meyer et al., 2023b), and the remaining two cross-sectional studies tested whether the response to treatment was predicted from baseline MRI patterns (Deckersbach et al., 2018; Ellard et al., 2018). As such, their design and statistical analysis pipelines were not comparable.

Second, two out of the six studies had overlapping samples (Meyer et al., 2023a, 2023b). As such, although the two works took into account different MRI outcome measures, the results might not be treated as totally independent.

Third, the samples had different diagnoses and comorbidities (i.e., BD I vs BD II; euthymic state *vs* current depressive episode, no comorbidities *vs* comorbid anxiety disorders). Also, information about the severity of the illness was not reported (e.g., age of onset; duration of illness, hospitalizations, etc.), and none of the studies controlled for pharmacotherapy effects in the analyses.

Fourth, the CBT protocols differed in terms of setting (individual vs group), length (8-to-24 weeks); theoretical framework (first-wave vs third-wave CBT vs integrated CBT intervention), and, in some cases, were poorly described.

Fifth, only functional (task-related or resting-state) neuroimaging studies were retrieved, thus precluding the conclusion of additional brain correlates of response to CBT (e.g., structural integrity, brain metabolisms). Furthermore, most studies adopted a ROI-based approach, focusing only on specific brain regions selected a priori.

Sixth, BD samples were not compared to other clinical groups with (partially) common neurobiological signatures (e.g., depression) (Gong et al., 2020). Thus, it was not possible to disentangle whether the neural changes associated with CBT are specific to BD.

Lastly, mirroring the discrepancy between the studies' objectives, a variety of outcome measures were used, such as fMRI-related tasks (mindfulness *vs* learning memory *vs* aToM); self-report questionnaires (i.e., HDRS, Beck Anxiety Index, FFMQ, Affective Control Scale, Difficulties in Emotion Regulation Scale, LIFE - Range of Impaired Functioning Tool), cognitive tests (i.e., digit span backward, delayed recall Rey's Complex Figure, Controlled Oral Word Association Test).

In conclusion, the present scoping review suggests, at the very preliminary level, the potential of CBT-based interventions in modulating neural activity and connectivity of bipolar patients, especially in regions underlying altered emotional response and social cognitive skills in BD patients (i.e., PFC, PCC, precuneus, amygdala, hippocampus, and insula). Nonetheless, the discrepancies between studies do not allow conclusions to be drawn. Therefore, this scoping review highlights the need to conduct future neuroimaging studies employing i) larger and better characterized bipolar samples with homogenous clinical manifestations; ii) multimodal imaging techniques that map distinct properties of neural integrity (e.g., brain anatomy, functional activity, and metabolism) and a whole-brain approach; iii) a longitudinal designs; iv) similar and better described CBT protocols and comparison interventions, v) comparison between patients with different mood disorders (e.g., unipolar *vs* bipolar depression) and vi) standardized tools to investigate the clinical response to treatments.

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CRediT authorship contribution statement

Francesca Girelli: Writing – original draft, Data curation, Conceptualization. **Maria Gloria Rossetti:** Writing – original draft, Data curation, Conceptualization. **Cinzia Perlini:** Writing – review & editing, Supervision. **Marcella Bellani:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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