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REVIEW ARTICLE

Neuronal underpinnings of cognitive impairment and - improvement in mood disorders†

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Neuropsychiatric illnesses including mood disorders are accompanied by cognitive impairment, which impairs work capacity and quality of life. However, there is a lack of treatment options that would lead to solid and lasting improvement of cognition. This is partially due to the absence of valid and reliable neurocircuitry-based biomarkers for pro-cognitive effects. This systematic review therefore examined the most consistent neural underpinnings of *cognitive impairment and cognitive improvement* in unipolar and bipolar disorders. We identified 100 studies of the neuronal underpinnings of working memory and executive skills, learning and memory, attention, and implicit learning and 9 studies of the neuronal basis for cognitive improvements. Impairments across several cognitive domains were consistently accompanied by abnormal activity in dorsal prefrontal (PFC) cognitive control regions—with the *direction* of this activity depending on patients' performance levels—and failure to suppress default mode network (DMN) activity. Candidate cognition treatments seemed to *enhance* task-related dorsal PFC and temporo-parietal activity when performance increases were observed, and to *reduce* their activity when performance levels were unchanged. These treatments also attenuated DMN hyper-activity. In contrast, nonspecific cognitive improvement following symptom reduction was typically accompanied by decreased limbic reactivity and reversal of pre-treatment fronto-parietal hyper-activity. Together, the findings highlight some common neural correlates of cognitive impairments and cognitive improvements. Based on this evidence, studies are warranted to examine the reliability and predictive validity of target engagement in the identified neurocircuitries as a biomarker model of pro-cognitive effects.

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Introduction

Unipolar disorder (UD) and bipolar disorder (BD) are among the leading causes of disability worldwide.[1] Common features of these mood disorders are persistent cognitive impairments across attention, memory, and executive function[2,3] and profound socio-occupational disability.[4–6] In particular, cognitive impairments directly contribute to patients' functional disability and high unemployment rates,[4–6] which constitute the largest socio-economic costs of mood disorders.[7,8]

Notwithstanding the clear need for treatment to target patients' cognitive impairments, there are no clinically available treatments with direct pro-cognitive efficacy in mood disorders.[9,10] Two recent systematic reviews of cognition trials revealed only preliminary evidence for potential efficacy of candidate treatments in UD and BD, respectively.[9,10] The disappointing findings are likely to result from common methodological challenges across cognition trials in mood disorders.[11] The International Society for Bipolar Disorder (ISBD) therefore convened an international task force to develop consensus-based recommendations for the design and methodology of cognition trials.[11] One of the important task force recommendations was to include neuroimaging assessments in future cognition trials to explore treatment-related target engagement in the neurocircuitries underlying patients' cognitive impairments. Insights from such assessments may provide a platform for identification of a sensitive neurocircuitry-based biomarker model that can *predict* treatment efficacy on cognition and thus serve as a surrogate endpoint in treatment development programs.

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Converging evidence from preclinical studies and neuroimaging studies in mood disorders suggest that cognitive impairments arise from disruption of neuroplasticity mechanisms and associated functional and structural changes in cognition-relevant neurocircuitries.[12] Specifically, functional magnetic resonance imaging (fMRI) studies have documented aberrant encoding and working memory–related activity in the medial and dorsal prefrontal cortex (PFC), and temporal and parietal regions during acute mood episodes and remission.[13–20] Patients' cognitive impairments may also be exacerbated by a failure to suppress neural activity in the default mode network (DMN), a network of medial brain regions implicated in self-referential thoughts and thought wandering.[14,21] In keeping with these findings, emerging evidence from a few recent intervention trials in mood disorders indicates that cognitive improvements are accompanied by neural activity changes in similar fronto-parietal, temporal, and DMN networks.[22–25] However, the precise location(s) and direction of the neural activity changes underlying cognitive *impairments* and cognitive *improvements* are unclear. The aims of the present systematic review were therefore to delineate (a) the most reliable neural underpinnings of cognitive impairments in mood disorders and (b) the emerging neural basis for direct or indirect cognitive improvements in response to candidate cognition treatments or reduction in mood symptoms, respectively.

Methods

Search strategy

The present systematic review followed the procedures of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[26] Systematic computerized searches were performed in the databases PubMed and PsycInfo from inception up until October 31, 2017 (see detailed search strategy in the Supplementary Material, available online). The title/abstract screening and subsequent full-text screening were performed by the authors. Disagreements were discussed and consensus reached in all cases.

Selection criteria

We included original research articles that examined the neural basis of cognitive impairment and/or improvement as measured with fMRI blood-oxygen-level-dependent (BOLD) techniques in adults with UD or BD irrespective of mood state. We excluded articles that (a) were not original (ie, meta-analyses and reviews), (b) were preclinical, (c) did not utilize the fMRI BOLD signal, (d) did not verify a diagnosis of UD or BD with either the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)[27] or the *International Classification of Diseases* (ICD),[28] and (e) examined pediatric/adolescent or geriatric populations. Articles were also excluded if (f) organic disease was present (including neurodegenerative diseases, brain tumors, head trauma, and brain surgery); (g) neuroimaging was not related to performance on an objective neuropsychological test; (h) they involved single-case reports; (i) they only relied on resting state fMRI; or (j) they examined the influence of genetic polymorphisms.

With regard to articles investigating *cognitive impairment*, we included studies with direct comparisons between UD or BD and healthy control (HC) groups, respectively. Regarding articles examining the neural underpinnings of *cognitive improvement*, we included trials assessing potential "direct" pro-cognitive effects on an intervention and those in which nonspecific cognitive improvement following symptom reduction was observed. In contrast, we excluded articles that (k) assessed cognitive *side-effects* of treatments. It was also an inclusion criterion for these trials that fMRI had been conducted both before and after treatment or, in the case of randomized controlled trials, at least after treatment completion.

Results

The systematic searches identified a total of 1362 unique articles after deletion of duplicates. An additional 9 references were identified from the reference lists of relevant reviews and meta-analyses. Based on the title/abstract screening, 141 articles were included in the full-text screening. Of these, 107 articles met the specified inclusion criteria and were included in the review. Figure 1 depicts the PRISMA flowchart of the screening procedure. The vast majority of studies (k = 100) examined the neural correlates of cognitive impairments, while only 9 studies investigated the neural basis of treatment-related cognitive improvement. Studies of the neural underpinnings of cognitive impairments were grouped into the following cognitive domains based on the employed fMRI paradigms: "working memory," "executive skills," "learning and memory," "attention," and "implicit learning." When the neural correlates of more than one relevant fMRI paradigm was reported in the same article, the results for each paradigm was presented under their respective cognitive domain. Similarly, articles investigating the neural correlates of both cognitive impairment and cognitive improvement appear twice in the respective tables.

Cognitive impairment

The design and findings of the 100 fMRI studies of cognitive impairments can be seen in Tables 1–3.[13,14,16,18,20,24,29–122]

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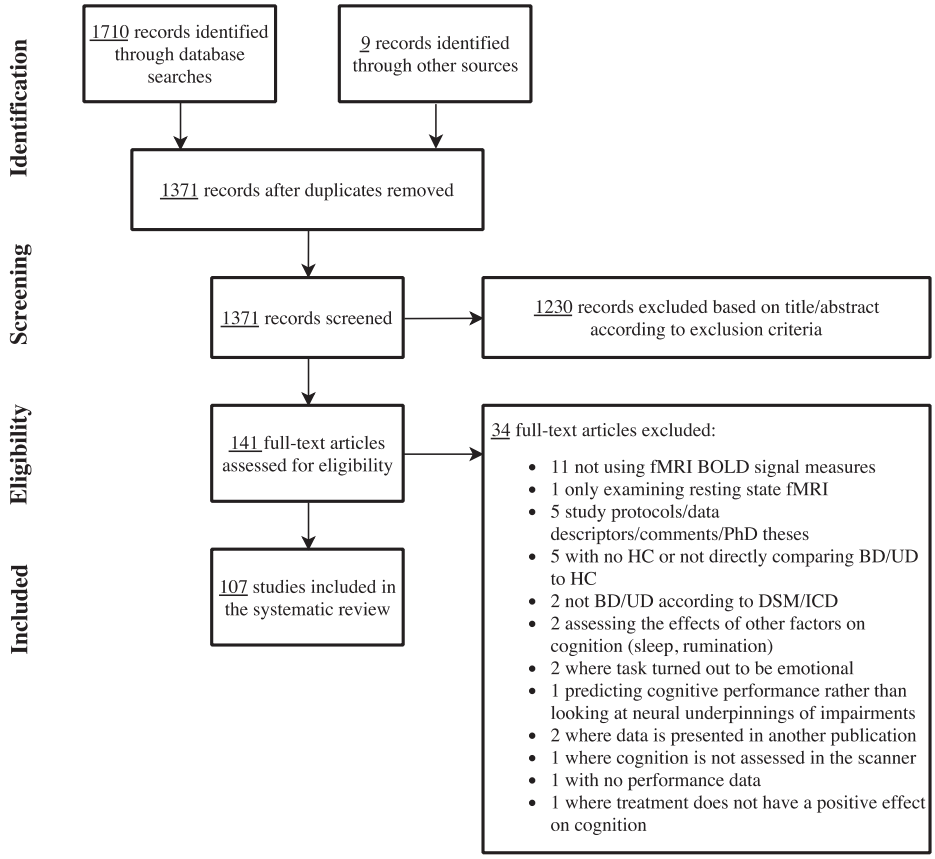

FIGURE 1. PRISMA flow chart. HC: Healthy control, BD: Bipolar disorder, UD: Unipolar disorder, DSM: Diagnostic and Statistical Manual of Mental Disorders (DSM),[27] ICD: International Classification of Diseases (ICD).[28]

The studies were distributed across the domains "working memory" (k = 37; Table 1), "executive skills" (k = 43; Table 2), "learning and memory" (k = 15; Table 3), "attention" (k = 6; Table 3), and "implicit learning" (k = 2; Table 3).

Working memory

Neural responses during working memory were assessed in 37 studies using a variety of fMRI paradigms, of which the most common ones were the n-back and delayed match-to-sample/Sternberg tasks. Twenty-two studies involved BD, 14 studies involved UD, and 1 study examined both groups (see Table 1).

Working memory in bipolar disorder. Thirteen (59%) studies reported impaired working memory performance in symptomatic and remitted BD patients (ie, poorer accuracy and/or slowed response times), whereas 9 (41%) studies found no performance impairment. The most robust findings were (i) *hypo*-activation in prefrontal cognitive control areas including the dorsolateral PFC (dlPFC)[14,16,20,32,51,70,74,75] and (ii) failure to deactivate regions within the DMN, most consistently the medial PFC[32,33,55,113] in BD relative to HC. These activity differences in cognitive control and DMN regions were commonly accompanied by impaired working memory performance.[14,24,32,33,70,74,75,101,113] In keeping with this, a study specifically comparing cognitively impaired with cognitively intact BD patients revealed *lower* dlPFC activation in the impaired group.[32] Another consistent finding was altered fronto-polar cortex activation in remitted BD, with studies indicating increased activation at low task loads and decreased activation at high task load.[29,45,63,101] Dorsolateral PFC *hypo*-activity thus seems to be linked to lower cognitive *capacity* (ie, impaired performance), while dlPFC *hyper*-activity may reflect lower cortical *efficiency* (ie, having to recruit more neural resources to maintain normal performance). Indeed, Adler *et al*[29] found that fMRI analyses co-varied for performance levels revealed task-related *hyper*-activation of fronto-polar cortex in remitted patients.

Finally, working memory performance in BD was also commonly associated with aberrant functional connectivity (FC) within subcortical and PFC structures as well as between subcortical structures and PFC,[74,81,96,113] although the findings regarding the *direction* of these FC changes were heterogeneous.

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TABLE 1. Summary of included studies for the cognitive domain: working memory

Author	Study design	Participants	fMRI paradigm	Findings
Gruber *et al* (2010)[55]	Case-control study	18 euthymic BD 1 and 18 HC. 83% of BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Articulatory rehearsal task	Performance: no difference. Activity: BD ↑ activation in right amygdala and in the right frontal cortex (precentral gyrus), intraparietal cortex, cerebellum, and frontal eye field.
McKenna *et al* (2014)[74]	Case-control study	23 euthymic BD 1 and 23 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Delayed match-to-sample task	Performance: poorer in BD. Activity: Encoding: ↓ in bilateral medial PFC and right dlPFC, bilateral caudate/thalamus/insula, and left middle temporal gyrus. Maintenance: BD ↑ right postcentral gyrus, right middle occipital cortex/middle temporal cortex, and bilateral cuneus. Connectivity: encoding: trend for diff. in functional connectivity between bilateral medial PFC and right IFG: medium effect size: BD ↑ connectivity >< HC.
Stegmayer *et al* (2015)[96]	Case-control study	18 euthymic BD and 18 HC. 83% of BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Delayed match-to-sample/ Sternberg task	Performance: trend toward poorer in BD in articulatory rehearsal task. Activity: BD ↓ negative functional connectivity between right amygdala and right precentral gyrus, right frontal eye field, and (pre)-SMA.
Monks *et al* (2004)[18]	Case-control study	12 euthymic BD 1 and 12 HC. BD medicated (mood stabilizers)	Delayed match-to-sample/ Sternberg task	Performance: No difference. Activity: No difference.
Lagopoulos *et al* (2007)[70]	Case-control study	10 euthymic BD and 10 HC. 70% of BD medicated (mood stabilizers)	Delayed match-to-sample/ Sternberg task	Performance: poorer in BD. Activity: Encoding: BD ↓ activity in right inferior frontal gyrus. Delay: BD ↓ activity in the right parahippocampal, inferior, and middle frontal gyri and ↑ activity in medial frontal gyrus. Response condition: BD ↓ activity in the superior frontal and anterior cingulate gyri.
Walter *et al* (2007)[108]	Case-control study	12 partially remitted UD and 17 HC. All UD medicated (antidepressants)	Delayed match-to-sample/ Sternberg task	Performance: poorer in UD for high cognitive loads. Activity: UD ↑ left dlPFC with highest cognitive load and ↑ activation in vmPFC during the control condition. Activity during *correct* trials also ↑ dlPFC in UD.
Vasic *et al* (2009)[105]	Case-control study	14 depressed UD and 14 HC. All UD medicated (antidepressants)	Delayed match-to-sample/ Sternberg task	Performance: poorer in UD, especially at high WM loads. Activity: UD ↓ functional connectivity in fronto-parietal network including inferior parietal, superior prefrontal, and frontopolar regions. UD ↑ functional connectivity in left dlPFC and bilateral cerebellum. In a temporally anti-correlated network, UD ↓ connectivity in the ACC, the vlPFC, and superior prefrontal cortex. UD ↑ connectivity in bilateral superior temporal cortex, left cuneus, and right lingual gyrus.
McKenna *et al* (2015)[75]	Case-control study	26 euthymic BD and 36 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Delayed match-to-sample task and N-task*	Performance: poorer in BD. Activity: BD: ↓ left dlPFC activity during encoding. Activity in bilateral dlPFC during encoding predicted performance in BD.
Robinson *et al* (2009)[88]	Case-control study	15 remitted BD and 15 HC. 93% of BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Delayed non-match-to-sample task	Performance: no difference. Activity: BD: ↑ retrieval-related activation in frontal regions and ↓ activation in parieto-occipital and temporal lobes. Novelty condition (encoding of new memories): BD ↓ activation in occipital and temporal lobe regions, posterior cingulate, left parahippocampal gyrus, left cuneus, bilateral fusiform gyrus and ↑ activity in right precentral gyrus, middle and inferior frontal gyrus, left medial frontal gyrus, and ACC.
Le *et al* (2017)[71]	Case-control study	18 unmedicated depressed UD and 21 HC	Delayed recognition task	Performance: poorer in UD. Activity: Retrieval scene > face contrast: UD ↓ activation in right and left transverse occipital sulcus/middle occipital gyrus and left posterior parietal. Memory-load effect weaker in UD. UD also aberrant retrieval-related functional connectivity between middle frontal gyrus and parahippocampal place area.
Townsend *et al* (2010)[20]	Case-control study	42 manic, euthymic or depressed BD and 14 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: no difference. Activity: BD ↓ right dlPFC activity, irrespective of mood state. BD ↓ right parietal activity, irrespective of mood state.
Wu *et al* (2014)[113]	Case-control (3 sample design)	20 BD-I in depression or remission and 29 HC (and 36 SZ). BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	N-back task	Performance: poorer in BD in 2-back task. Activity: BD ↑ activity in left posterior cingulate cortex and medial PFC in 2-back task (less deactivation in BD >< HC). Aberrant effective connectivity in BD: positive from left PCC to mPFC and negative from mPFC to PCC.

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TABLE 1. Continued

Author	Study design	Participants	fMRI paradigm	Findings
Thermenos *et al* (2010)[101]	Case-control study	19 stable BD, 18 relatives, and 19 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	N-back task	Performance: poorer in BD. Activity: BD and relatives ↑ activation in left anterior insula (less deactivation). BD ↓ left frontopolar cortex activity >< HC and relatives.
Adler *et al* (2004)[29]	Case-control study	15 euthymic BD and 15 HC. 67% of BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: poorer in BD. Activity: BD ↑ activation in frontopolar cortex, basal ganglia, thalamus, temporal cortex, and posterior parietal cortex (when covarying for performance) and ↓ activation in posterior cingulate.
Brooks *et al* (2015)[38]	Case-control study	19 depressed BD 2 and 19 HC. BD unmedicated	N-back task	Performance: no difference. Activity: BD ↓ activation in left middle frontal gyrus, left superior frontal gyrus, left inferior parietal lobule, left middle temporal gyrus/angular gyrus, and bilateral occipital regions.
Fernández-Concuera *et al* (2013)[14]	Case-control study	41 depressed BD and 41 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: Poorer in BD. Activity: BD ↓ activation in bilateral dlPFC and cerebellum.
Drapier *et al* (2008)[45]	Case-control study	20 remitted BD 1, 20 relatives, and 20 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: poorer in BD (>< HC and relatives). Activity: BD ↑ activation during 1-back in frontal pole and in right parietal lobe/precuneus ↑ activation in right and left parietal lobe/precuneus during 2-back.
Jogia *et al* (2012)[63]	Case-control study	36 euthymic BD 1 and 37 HC. 61% of BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: no difference. Activity: BD ↑ activation in right superior and middle temporal gyri during high-load (3-back), and in ↑ vlPFC during low to medium loads (0-2-back) and ↓ vlPFC activation during high load (3-back).
Palaniyappan *et al* (2014)[81]	Case-control study	20 stable, psychotic BD and 34 HC (and 39 SZ). BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: poorer in BD. Activity: BD: ↑ degree of centrality in the hippocampus/parahippocampus and in thalamic regions and lateral parietal cortex and ↓ connectivity of the right insula.
Dell'Osso *et al* (2015)[42]	Case-control study	28 euthymic BD (15 BD 1, 13 BD 2) and 27 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: no difference. Activity: BD ↑ right middle frontal gyrus engagement regardless of WM load. Especially, BD 1 had greater BOLD signal change, while BD 2 expressed an intermediate pattern of activation.
Alonso-Lana *et al* (2016)[32]	Case-control (3 sample design)	50 euthymic BD (27 cognitively preserved, 23 cognitively impaired) and 28 HC. BD (both groups) medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: poorer in all patients >< HC. Activity: cognitively impaired patients ↓ right dlPFC than cognitively preserved patients during high-load WM. Both patient groups ↑ activation in medial frontal cortex (failure to deactivate) >< HC.
Alonso-Lana *et al* (2016)[33]	Case-control (3 sample design)	20 euthymic BD, 20 relatives, and 40 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: poorer in BD. Activity: BD (and relatives) ↑ activity (failure to deactivate) cluster in medial PFC during WM (less marked in relatives).
Monks *et al* (2004)[18]	Case-control study	12 euthymic BD 1 and 12 HC. BD medicated (mood stabilizers)	N-back task	Performance: No difference. Activity: BD ↓ bilateral frontal, temporal, and parietal activation (anterior cingulate gyrus, right medial frontal and middle temporal gyrus and bilaterally in the inferior frontal gyrus, middle frontal gyrus, precuneus, and cerebellar regions). BD ↑ activity in left precentral, right medial frontal and left supramarginal gyri.
Brandt *et al* (2014)[37]	Case-control study	100 euthymic, psychotic, elevated or depressed BD and 100 HC (and 100 SZ). BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	N-back task	Performance: poorer in BD. Activity: no difference in any components in BD >< HC.
Frangou (2005)[51]	Case-control study	7 remitted BD 1 and 7 HC (43 of each in the study but only a subsample undergoes fMRI). BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: no difference. Activity: BD ↓ activity in dorsal PFC and anterior cingulate and ↑ in another part of superior frontal PFC during high memory demands.
Fitzgerald *et al* (2008)[48]	Case-control study	13 depressed UD and 13 HC. 85% of UD medicated (antidepressants)	N-back task	Performance: no difference. Activity: UD ↑ bilateral activity in middle, medial, inferior frontal gyri, anterior cingulate gyrus, precentral gyrus, inferior parietal lobule, superior temporal gyrus, cuneus/precuneus, and thalamus. UD ↑ right orbital gyrus and left middle temporal gyrus.
Bartova *et al* (2015)[35]	Case-control study	78 remitted UD and 42 HC. UD unmedicated	N-back task	Performance: no difference. Activity: UD ↑ DMN activity (less deactivation) during WM; strongest differences in the

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TABLE 1. Continued

Author	Study design	Participants	fMRI paradigm	Findings
				anterior-medial (am) PFC. Activation patterns of adult-onset UD did not sig. differ from HC. Adolescent-onset UD (>< HC) ⬇ functional coupling between amPFC and medial, middle, and superior frontal gyrus and precuneus and ⬆ amPFC-dlPFC coupling. Adult-onset UD: qualitatively similar, but less-pronounced.
Garrett *et al* (2011)[52]	Case-control study	16 depressed, psychotic UD, 16 depressed, nonpsychotic UD, and 19 HC. UD medicated (antidepressants, mood stabilizers, antipsychotics and/or benzodiazepines)	N-back task	Performance: poorer in non-psychotic UD (>< HC). Activity: Both psychotic and non-psychotic UD ⬆ activation in the right parahippocampal gyrus. Nonpsychotic UD ⬇ activity in right dlPFC (>< other groups) and ⬆ in the right superior occipital cortex (>< HC). Psychotic UD ⬆ right temporo-parietal activity (>< other groups).
Matsuo *et al* (2007)[73]	Case-control study	15 depressed UD and 15 HC (only performance data for 10 HC, 9 UD). UD unmedicated	N-back task	Performance: no difference. Activity: UD ⬆ left dlPFC, middle and superior frontal gyrus activation (>< HC).
Norbury *et al* (2014)[78]	Case-control study	15 remitted UD and 15 HC. UD unmedicated	N-back task	Performance: no difference. Activity: Quadratic load: UD showed a positive quadratic load response in the bilateral hippocampus; the converse was true for HC. UD ⬆ activity in bilateral hippocampus (less deactivation >< HC).
Rodriguez-Cano *et al* (2014)[89]	Case-control study	26 depressed UD and 52 HC. UD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	N-back task	Performance: poorer in UD. Activity: 2-back vs. baseline: UD ⬇ activation in the left dlPFC, extending to the precentral gyrus and the frontal operculum, also incl. left and right thalamus and left caudate. 2) cluster in the precuneus, reaching the cuneus and bilateral superior parietal cortex 3 +4) clusters in the cerebellum which also reached the left inferior occipital cortex. UD ⬆ medial frontal cortex and perigenual anterior cingulate cortex (reduced deactivation >< HC).
Schöning *et al* (2009)[94]	Case-control study	28 euthymic UD and 28 HC. UD medicated (antidepressants)	N-back task	Performance: no difference. Activity: UD ⬆ cingulate cortex activity; dlPFC and vlPFC activation comparable between UD and HC.
Barch *et al* (2003)[34]	Case-control study	14 depressed UD and 49 HC (and 38 SZ). Only 14% of UD patients were medicated (antidepressants)	N-back task	Performance: no difference. Activity: UD ⬇ activity in bilateral thalamus, right precentral gyrus, and right parietal cortex.
Rose *et al* (2006)[90]	Case-control study	9 symptomatic UD patients on antidepressant medication and 9 HC	N-back task	Performance: no difference. Activity: UD ⬆ activity in medial orbitofrontal cortex/rostral ACC.
Harvey *et al* (2005)[60]	Case-control study	10 moderately to severely depressed UD and 10 HC. UD medicated (antidepressants and/or benzodiazepines). All tested within the first 2 weeks of the antidepressant treatment.	N-back task	Performance: no difference. Activity: UD ⬆ activation of the left inferior and middle frontal gyrus and the dorsal anterior cingulate.
Hammar *et al* (2016)[59]	Case-control study	17 remitted or partially remitted UD and 17 HC. UD medicated (not specified)	N-back task	Performance: poorer in UD. Activity: no diff. in activation in ACC or dlPFC. UD ⬇ caudate and putamen. No correlations between brain responses and performance.
Meusel *et al* (2013)[24]	Case-control study, nonrando-mized clinical trial	35 partially remitted BD/UD and 15 HC. BD/UD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	N-back task	Performance: poorer in UD/BD. Activity: patients ⬇ activation in superior frontal gyrus during 2-back vs. 0-back conditions.
Hamilton *et al* (2009)[16]	Case-control study	21 euthymic BD 1 and 38 HC (and 20 SZ). 81% of BD patients medicated (antidepressants, mood stabilizers, and/or antipsychotics)	WM fMRI paradigm from the Functional Reference Battery	Performance: no difference. Activity: BD ⬇ activity in occipital regions incl. right primary visual cortex.

Abbreviations: HC: Healthy control, BD: Bipolar disorder, UD: Unipolar disorder, SZ: Schizophrenia, PFC: prefrontal cortex, mPFC: medical PFC, lPFC: lateral PFC, dlPFC: dorsolateral PFC, vmPFC: Ventromedial PFC, amPFC: Anterior medial PFC, SMA: Supplementary motor area, PCC: posterior cingulate cortex, STG: Superior temporal gyrus, WM: Working memory, ><: Compared to.

* The authors combined the results from the two fMRI tasks for an overall working memory score.

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TABLE 2. Summary of included studies for the cognitive domain: executive skills

Author	Study design	Participants	fMRI paradigm	Findings
Frangou (2011)[50]	Case-control study	46 euthymic BD 1, 48 relatives, and 71 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Color-word Stroop task	Performance: no difference. Activity: BD ⬇ activation in superior parietal lobule, the inferior parietal lobule, the head of the caudate, and the vlPFC. BD: ⬇ functional connectivity between the vlPFC, ACC, and insula.
Pompei *et al* (2011)[84]	Case-control study	39 euthymic BD 1, 39 relatives (25 healthy, 14 UD), and 48 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics). UD relatives unmedicated	Color-word Stroop task	Performance: no difference. Activity: BD and relatives (>< HC): ⬇ response in posterior and inferior parietal lobules (no difference. between relatives and BD). Left caudate mean activation ⬇ in BD >< HC and relatives without Axis I diagnosis. Right inferior frontal gyrus mean level activation ⬇ in BD >< all other groups incl. UD relatives.
Kronhaus *et al* (2006)[69]	Case-control study	10 euthymic BD (some with residual depression) and 11 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Color-word Stroop task	Performance: no difference. Activity: BD ⬇ activation of visual and left dl- and vlPFC areas. BD ⬇ left orbital and medial prefrontal cortices.
Blumberg *et al* (2003)[36]	Case-control study	36 elevated, depressed, or euthymic BD 1 and 20 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines).	Color-word Stroop task	Performance: no difference. Activity: BD ⬇ activation in left rostral ventral PFC independent of mood state. Right ventral PFC: ⬇ increase in elevated mood >< euthymic, left ventral PFC: ⬆ increase in signal in depressed group >< euthymic group.
Gruber *et al* (2004)[57]	Case-control study	11 stable BD and 10 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Color-word Stroop task	Performance: interference task poorer in BD. Activity: interference task: BD: ⬇ signal intensity in right anterior cingulate (attention to action area). BD: ⬆ dlPFC activation.
Pompei *et al* (2011)[83]	Case-control study	39 euthymic BD 1, 39 relatives (25 healthy, 14 UD), and 48 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics). UD relatives unmedicated	Color-word Stroop task	Performance: no difference. Activity: BD (and relatives >< HC) ⬇ dlPFC connectivity with vACC. BD: positive vlPFC-insula connectivity (negative connectivity in HC). ⬇ vlPFC-basal ganglia connectivity in BD and UD relatives.
Marchand *et al* (2007)[72]	Case-control study	14 depressed BD 1 and 15 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Color-word Stroop task	Performance: no difference. Activity: BD ⬇ activity in bilateral posterior cingulate and occipital cortex.
Taylor *et al* (2016)[100]	Case-control (3 sample design)	16 UD in different phases and 16 HC (and 16 SZ). 63% of UD medicated (antidepressants)	Color-word Stroop task	Performance: UD ⬇ cognitive workload capacity >< HC. Activity: UD (and SZ) ⬇ functional connectivity between ACC, parietal, and temporal hubs.
Kikuchi *et al* (2012)[67]	Case-control study	42 depressed UD and 17 HC. UD unmedicated	Color-word Stroop task	Performance: no difference. Activity: UD: ⬇ activation during incongruent blocks in middle frontal gyrus, paracingulate and posterior cingulate, precuneus, occipital regions, and brain stem.
Wagner *et al* (2010)[106]	Prospective, naturalistic open-label design	20 depressed UD and 20 HC. UD medicated (benzodiazepines)	Color-word Stroop task	Performance: no difference. Activity: UD ⬆ froto-parieto-temporal network and rostral ACC in the incongruent condition.
Wagner *et al* (2006)[107]	Case-control study	16 depressed UD and 16 HC. UD unmedicated	Color-word Stroop task	Performance: no difference. Activity: interference condition: UD ⬆ activity in rostral anterior cingulate gyrus and left dlPFC; correlated with the Stroop interference. Congruent condition: no difference. in activity UD >< HC
Schlösser *et al* (2008)[93]	Case-control study	16 depressed UD and 16 HC. UD unmedicated	Color-word Stroop task	Performance: no difference. Activity: UD ⬆ dACC to rACC connectivity. UD: ⬆ task-related input from the dACC to rACC.
Strakowski *et al* (2005)[99]	Case-control study	16 euthymic BD and 16 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Counting Stroop interference task	Performance: poorer in BD. Activity: BD: ⬇ activation in temporal cortical regions (inferior, middle and superior temporal gyrus), middle frontal gyrus, vlPFC, putamen and midline cerebellum. BD ⬆ medial occipital cortex. (HC: activation in right middle temporal gurys = negatively correlated w. percentage of correct responses and pos. corr. with false hits; BD: reverse association.)
Roth *et al* (2006)[91]	Case-control study	11 mixed state, manic, depressed, or euthymic BD 1 and 11 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Counting Stroop interference task	Performance: No difference. Activity: BD ⬇ activation in right inferior gyrus, right pons, left posterior cingulate, fusiform, parahippocampal, and middle occipital gyri. BD ⬇ right posterior medial frontal gyrus.

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TABLE 2. Continued

Author	Study design	Participants	fMRI paradigm	Findings
Penfold *et al* (2015)[82]	Case-control study	19 depressed BD 2 and 20 HC. BD unmedicated	Go/no-go task	Performance: no difference. Activity: NoGo > Go contrast: BD (>< HC)⬇ frontal activation in right inferior frontal gyrus, right middle frontal gyrus, superior frontal gyrus, insula, and bilateral precentral gyrus. BD:⬇ activation in the temporal and occipital lobes.
Joshi *et al* (2016)[64]	Case-control study	45 euthymic BD 1 and 45 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Go/no-go task	Performance: no difference. Activity: During response inhibition, BD ⬇ left prefrontal areas, right inferior parietal lobule, and left globus pallidus.
Strakowski *et al* (2008)[97]	Case-control study	19 manic BD 1 and 17 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Go/no-go task	Performance: no difference. Activity: response inhibition: BD ⬇ activation in anterior and posterior cingulate, medial dorsal thalamus, middle temporal gyrus, and precuneus.
Mazzola-Pomietto *et al* (2009)[118]	Case-control study	16 manic BD and 16 HC. BD medicated (mood stabilizers and/or antipsychotics)	Go/no-go task	Performance: poorer in BD in Go-trials. Activity: BD ⬇ vlPFC during response inhibition.
Welander-Vatn *et al* (2009)[122]	Case-control study	27 euthymic, mildly or moderately/severely depressed BD 2 and 28 HC. 59% of BD medicated (antidepressants and/or mood stabilizers)	Go/no-go task	Performance: no difference. Activity: no difference.
Townsend *et al* (2012)[121]	Case-control study	32 euthymic BD 1 and 30 HC. 72% of BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Go/no-go task	Performance: no difference. Activity: BD: ⬇ activation in bilateral inferior frontal cortex, left medial frontal gyrus, left inferior and superior parietal lobe, bilateral putamen, bilateral caudate, bilateral globus pallidus, right thalamus, and right subthalamic nucleus. No areas of greater activation in BD.
Wessa *et al* (2007)[112]	Case-control study	17 euthymic BD and 17 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Go/no-go task	Performance: no diff. Activity: no diff.
Ajilore *et al* (2015)[30]	Case-control study	16 euthymic BD 1 and 16 HC. 88% of BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Go/no-go task	Performance: poorer in BD. Activity: BD ⬇ vlPFC activation during No-Go minus Go, driven primarily by the right side.
Welander-Vatn *et al* (2013)[110]	Case-control study	24 euthymic, depressed, or mixed manic/depressed BD 1 and 24 HC. BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Go/no-go task	Performance: poorer in BD. Activity: no difference. In either full brain analysis or region of interest approach.
Altshuler *et al* (2005)[115]	Case-control study	11 manic BD 1 and 13 HC. BD medicated (mood stabilizers and/or antipsychotics)	Go/no-go task	Performance: no difference. Activity: BD ⬇ activation in right lateral orbitofrontal cortex, right lPFC, and right hippocampus. BD ⬇ activation in left rostral cingulate.
Fleck *et al* (2011)[116]	Case-control study (3-sample design)	20 mixed episode or depressed BD 1 and 10 HC. 75% of BD medicated (not specified)	Go/no-go task	Performance: Poorer in BD. Activity: BD-Mixed ⬆activation of right amygdala and frontal cortex (>< HC). BD-mixed ⬆left thalamus, left cerebellum, and right inferior frontal gyrus (>< BD-Depressed).
Kaladjian *et al* (2009)[117]	Case-control study	20 euthymic BD 1 and 20 HC. BD medicated (mood stabilizers and/or antipsychotics)	Go/no-go task	Performance: no difference. Activity: BD ⬇ activation in left frontopolar cortex and bilateral dorsal amygdala during response inhibition.
Korgaonkar *et al* (2013)[68]	Case-control study	30 depressed UD and 30 HC. UD antidepressant medication naïve	Go/no-go task	Performance: poorer in UD. Activity: UD ⬆ ACC during response inhibition.
Crane *et al* (2016)[40]	Case-control (3 sample design)	47 depressed UD (29 UD + anxiety) and 54 HC. UD unmedicated	Go/no-go task	Performance: poorer in UD on Go-trials. Activity: UD ⬇ right inferior frontal gyrus during commissions and ⬇ throughout the brain (superior and middle frontal regions, posterior cingulate, cuneus, fusiform, and caudate) during rejection.
Rao *et al* (2015)[85]	Case-control study (4-sample design)	16 depressed UD and 18 HC (and 20 geriatric UD and 17 geriatric HC). 32% of UD medicated (not specified)	Go/no-go task	Performance: poorer in UD. Activity (during correct hits): UD ⬆ activation in the left cuneus >< HC.
Ryan *et al* (2015)[92]	Case-control study		Go/no-go task	Performance: poorer in BD and UD (BD worse). Activity: BD and UD: ⬆ activation in left superior temporal

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TABLE 2. Continued

Author	Study design	Participants	fMRI paradigm	Findings
		19 depressed or euthymic UD, 16 depressed or euthymic BD, and 17 HC. Medication not specified		gyrus and right superior parietal lobule and cerebellum (>< HC). Activity for UD > HC > BD in middle frontal, medial frontal, dorsal anterior cingulate, posterior cingulate, and cuneus. BD ⬆ > UD > HC in precuneus. UD ⬆ dorsal cingulate, precuneus, middle temporal, insula, and declive. HC and UD: ⬆ activity in these areas positively correlated with performance.
McIntosh *et al* (2008)[119]	Case-control study (3-sample design)	42 euthymic BD 1 and 37 HC (and 27 SZ). BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Hayling Sentence Completion Test	Performance: no difference. Activity: Active vs. Rest: BD ⬇ left insula. Parametric analysis of increasing sentence constraint: BD ⬆ right vlPFC, right ventral striatum, and left caudal middle temporal gyrus. Reversal learning errors were sig. neg. associated response in both orbitofrontal and ventral striatal regions in BD (not in HC).
Gruber *et al* (2017)[56]	Case-control study	29 euthymic BD (some with residual depressive symptoms) and 21 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Multi-source interference task	Performance: poorer in BD across conditions. Activity: interference-control contrast: BD ⬇ activity in anterior and middle cingulate cortex. BD: ⬆ activation in left inferior frontal gyrus (dlPFC) >< HC.
Weathers *et al* (2013)[109]	Case-control study (4-sample design)	23 euthymic, depressed, hypomanic, or mixed state BD and 27 HC (and 15 pediatric BD and 20 pediatric HC). BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Response flexibility paradigm	Performance: poorer in BD. Activity: BD ⬇ frontal, parietal, and temporal activation >< HC during successful alternate response and ⬇ precuneus, middle, and superior temporal gyri and inferior parietal activation in BD during successful change.
Remijnse *et al* (2013)[86]	Case-control study	19 depressed UD and 29 HC (and 18 OCD). UD unmedicated	Self-paced letter/digit task switching paradigm	Performance: poorer in UD. Activity: UD ⬇ right anterior PFC and right inferior parietal activation during switching. No area of increased activations in UD.
van Tol *et al* (2011)[104]	Case-control study	65 remitted, mildly depressed, or moderately/severely depressed UD, 82 UD + anxiety, and 64 HC (and 64 anxiety). 25% of UD medicated (antidepressants)	Tower of London task	Performance: No difference. Activity: moderately/severely depressed: ⬆ left dlPFC as a function of task load. Mildly depressed and remitted UD: no difference.
Fitzgerald *et al* (2008)[48]	Case-control study	13 depressed UD and 13 HC. 85% of UD medicated (antidepressants)	Tower of London task	Performance: poorer in UD. Activity: UD ⬆ right inferior and middle frontal gyrus and right angular gyrus/cuneus.
Rive *et al* (2016)[87]	Case-control study (5-sample design)	40 remitted or depressed UD, 32 remitted or depressed BD, and 35 HC. UD and BD unmedicated	Tower of London task	Performance: no difference. Activity: Linear relationship between increase in activity and task load: patients > HC: IPG/SPG/postcentral gyrus. Differences between patients: task > baseline: ⬆ dlPFC activity in remitted UD >< remitted BD. Depressed BD ⬆ activity >< depressed UD in dlPFC and in caudate (depressed BD ⬆ caudate >< HC, depressed UD and remitted BD ⬇ >< HC).⬆dlPFC activity in remitted UD >< depressed UD. [HC looks sig. diff. >< remitted UD and maybe also depressed BD (hyper-activation >< HC) and depressed UD (hypo-activation >< HC)].
Curtis *et al* (2007)[41]	Case-control study	12 euthymic BD and 12 HC. BD medicated (mood stabilizers)	Phonetic lexical decision task: rhyming task, semantic lexical decision task, phonetic verbal fluency task, semantic verbal fluency task	Performance: poorer in BD. Activity: BD showed ⬆ activation in left PFC and bilateral cerebellum/fusiform/lingual gyrus cluster (medial occipital cortex). BD: ⬇ activity in medial frontal cortex incl. ACC. BD ⬆ PFC response to high-demand tasks compared to low-demand tasks (>< HC).
Yoshimura *et al* (2014)[114]	Case-control study	10 euthymic BD 1 and 10 HC. BD medicated (mood stabilizers and/or antipsychotics)	Verbal fluency task	Performance: no difference. Activity: BD ⬆ activation in the bilateral precuneus.
Allin *et al* (2010)[31]	Case-control study	18 remitted BD, 19 relatives, and 19 HC. 74% of BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Verbal fluency task	Performance: poorer in BD. Activity: BD ⬆ activation in the posterior cingulate cortex and ⬇ left PFC activity (>< HC).
Costafreda *et al* (2011)[39]	Case-control study	32 euthymic BD and 40 HC (and 32 SZ). 81% of BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Verbal fluency task	Performance: no difference. Activity: BD ⬆ activation in dorsal anterior cingulate, dlPFC, and right putamen (intermediate that of HC and SZ). BD ⬆ activity in the precuneus, posterior cingulate, and angular gyrus (⬇ deactivation).

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TABLE 2. Continued

Author	Study design	Participants	fMRI paradigm	Findings
Okada *et al* (2003)[120]	Case-control study	10 depressed UD and 10 HC. UD medicated (antidepressants)	Verbal fluency task	Performance: poorer in UD. Activity: UD ⬇ activation of ACC and inferior frontal gyrus.
Hugdahl *et al* (2004)[61]	Case-control study	12 depressed UD and 12 HC (and 12 SZ). UD medicated (antidepressants)	Vigilance task and a mental arithmetic task	Performance: poorer in UD in both tasks. Activity: UD ⬆ activity in middle frontal gyrus. UD: ⬇ activation in the right inferior parietal lobule.

Abbreviations: HC: Healthy control, BD: Bipolar disorder, UD: Unipolar disorder, SZ: Schizophrenia, OCD: Obsessive compulsive disorder, PFC: prefrontal cortex, dlPFC: dorsolateral PFC, vlPFC: ventrolateral PFC, ACC: Anterior cingulate cortex, vACC: Ventral ACC, rACC: rostral ACC, Anterior cingulate gyrus, IPG: inferior parietal gyrus, SPG: superior parietal gyrus, sig. diff: Significant difference, > <: Compared to.

Working memory in unipolar disorder. Six (43%) studies found working memory impairments in symptomatic and remitted UD,[52,59,71,89,105,108] while 8 (57%) showed comparable performance in UD and HC.[34,35,48,60,73,78,90,94] As with BD, the most consistent neural activation differences during working memory were altered response of cognitive control areas, most consistently in the dlPFC[48,52,60,73,89,108] and impaired deactivation of DMN regions, including the medial PFC.[35,89,90]

Of 6 studies in symptomatic and partially remitted patients, 2 studies found dlPFC *hypo*-activation, which was associated with impaired performance,[52,89] while another 4 found dlPFC *hyper*-activity that was accompanied by preserved performance.[48,60,73,108] However, this association between direction of dlPFC activity and performance was not uniform; 3 studies reported no increase in dlPFC in remitted patients with intact working memory performance,[34,78,94] and 1 study found no dlPFC hypo-activation in cognitively impaired patients.[59] Notably, 2 of the 3 studies showing intact working memory performance and normal dlPFC activity were conducted in remitted patients, suggesting that cognitive and neural functioning is normalized after remission in some UD patients[34,94]. Finally, symptomatic and remitted UD patients were found to display altered FC within PFC regions and between PFC and parietal nodes of the cognitive control network.[35,71,105]

Executive skills

Forty-three studies examined executive skills using a variety of different tasks, most commonly the Stroop, Go/No-Go, Tower of London, and Verbal fluency tasks. Twenty-eight studies were conducted in patients with BD and 13 in patients with UD, while 2 studies examined both populations (see Table 2).

Executive skills in bipolar disorder. Seventeen (61%) studies in BD reported no behavioral differences from HC, while 11 (39%) studies demonstrated poorer performance in BD (see Table 2). Of these, most studies that reported no behavioral differences were conducted in remitted patients.

A highly consistent finding across 75% of the studies was *hypo*-activity within a distributed cognitive control network including vlPFC/inferior frontal gyrus, dlPFC, and inferior and superior parietal areas, which appeared to be largely independent of mood state and performance levels,[30,31,36,39,50,64,69,82,84,91,92,99,109,115,117,118,121] with only 25% of studies reporting *hyper*-activation in these regions.[41,56,57,87,116,119] Hypo-activation was particularly pronounced in prefrontal, parietal, and striatal regions.[30,31,36,50,64,69,82,84,91,99,109,115,117,118,121] The findings indicate that hypo-activation in the cognitive control network in BD can occur even when the task load does not exceed patients' cognitive capacity.

Abnormal task-related anterior cingulate cortex (ACC) activity, particularly in the dorsal part, was also reported in multiple BD studies across mood states. Again, the majority of these studies reported hypo-activation,[41,56,57,92,97,115] while 2 reported hyper-activation[39] or no differences.[110] A final replicated finding was decreased task-related ventral ACC-PFC FC in remitted BD.[50,83]

Executive skills in unipolar disorder. Nine (69%) studies of UD found impaired task performance,[40,48,61,68,85,86,100,104,120] particularly in patients with greater depression severity,[104] while 4 (31%) studies[67,93,106,107] reported no behavioral differences. These studies were almost all conducted in symptomatic patients. In general, patients exhibited *hypo*-activation in prefrontal and parietal cognitive control regions when performance was impaired and *hyper*-activation in this network when performance was preserved,[40,86,87,104,106,107,120] although 2 studies found *hyper*-activity in these regions in patients with impaired performance.[48,92] The areas with most consistent activation abnormalities were inferior, middle, and frontal gyrus; anterior PFC; dlPFC; and inferior parietal cortex. In addition, symptomatic patients also

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TABLE 3. Summary of included studies for the cognitive domains: learning and memory, attention, and implicit learning

Author	Study design	Participants	fMRI paradigm	Findings
Learning and memory				
Glahn *et al* (2010)[54]	Case-control study	15 remitted BD 1 and 24 HC. 93% of BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Associative learning paradigm	Performance: no difference. Activity: BD: ⬇ encoding-related activation in left inferior frontal gyrus, cingulate gyrus, superior parietal lobule, right insular cortex, lentiform nucleus, and bilateral occipital and cerebellum and ⬆activation in left middle frontal gyrus, precuneus, and left superior temporal gyrus. BD ⬇ retrieval-related left hippocampus and parahippocampal gyrus, bilateral cerebellum, bilateral sensory-motor regions. Region of interest analyses: BD ⬆ encoding-related and ⬇ retrieval-related activity in dlPFC.
Hall *et al* (2010)[58]	Case-control study	14 stable BD 1 and 14 HC (and 15 SZ). BD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Associative learning paradigm	Performance: no difference (was matched). Activity: BD ⬇ activation in left dlPFC during encoding >< HC (and SZ).
Werner *et al* (2009)[111]	Case-control study	11 depressed UD and 11 HC. UD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Associative learning paradigm	Performance: no difference. Activity: UD ⬆ encoding-related activity in superior part of left parahippocampal gyrus and ⬇ activity in frontal and parietal regions. UD ⬇ retrieval-related activation in ACC and parietal areas and ⬆ activity in left superior frontal gyrus and right fusiform gyrus.
Fairhall *et al* (2010)[46]	Case-control study	8 depressed UD and 8 HC. 75% of UD medicated (antidepressants and/or benzodiazepines)	Associative learning paradigm	Performance: no difference. Activity: significant group × condition interaction in bilateral anterior hippocampus: positive relationship between hippocampal activity and successful encoding in HC; not present in UD. UD: dysregulated memory related hippocampal function rather than hypo- or hyper-activation of hippocampus per se.
Oertel-Knöchel *et al* (2014)[80]	Case-control study	21 remitted BD 1 and 20 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Computer-based nonverbal learning and recognition test	Performance: poorer in BD. Activity: BD ⬇ encoding-related activity in bilateral ACC, precuneus/cuneus, and left lingual gyrus. BD ⬆ activation (⬇ deactivation) in left temporo-parietal junction and ⬇ ventral hippocampal activation during retrieval.
Dietsche *et al* (2014)[13]	Case-control study	23 depressed UD and 23 HC. UD medicated (antidepressants and/or antipsychotics)	Non-emotional episodic memory encoding and retrieval task	Performance: poorer in UD. Activity: UD ⬇ encoding-related activation in right middle and medial frontal gyrus, right cingulate cortex, hippocampus, and parahippocampal gyrus. UD ⬆ retrieval-related activation in the right inferior frontal gyrus. Lack of "normal" association between encoding-related hippocampal activation and retrieval success in UD.
Kassel *et al* (2016)[65]	Case-control study	42 UD in different phases and 40 HC. 41% of UD medicated (not specified)	Semantic list learning task	Performance: poorer in UD. Activity: UD ⬇ encoding-specific activation in bilateral middle frontal gyrus, dorsal ACC, insula, precuneus, superior parietal lobule, thalamus, and cerebellum.
van Eijndhoven *et al* (2013)[102]	Case-control study	40 recovered or depressed medication free UD and 20 HC	Source recollection paradigm and Picture encoding and recognition task	Performance: no difference. Activity: symptomatic UD ⬆ retrieval-related activity in left inferior frontal gyrus.
van Eijndhoven *et al* (2011)[103]	Case-control study	40 recovered or depressed UD and 20 HC. Depressed subgroup: antidepressant medication naïve and recovered subgroup medication-free	Source recollection paradigm and Picture encoding and recognition task	Performance: no difference. Activity: symptomatic patients ⬆ activation in left inferior frontal gyrus, left insula, posterior cingulate, precuneus, caudate nucleus, and bilateral thalamus >< HC and remitted patients. Greater memory-related right amygdala activity in all patients (>< HC).
Finkelmeyer *et al* (2016)[47]	Case-control study	20 depressed UD and 20 HC. UD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Spatial memory task	Performance: no difference. Activity: UD failed to show normal task-dependent changes bilateral anterior hippocampus activity but no activity differences in the whole-brain analyses.

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TABLE 3. Continued

Author	Study design	Participants	fMRI paradigm	Findings
Milne *et al* (2012)[76]	Case-control study	22 euthymic UD and 18 HC. 86% of UD medicated (antidepressants, mood stabilizers, and/or antipsychotics)	Recollection memory process dissociation task	Performance: poorer in UD. Activity: UD ⬇ activation of the right hippocampal and left parahippocampal gyrus during recollection. (Recollection memory performance was corr. with changes in right hippocampus BOLD signal in HC; but not UD.)
Meusel *et al* (2013)[24]	Case-control study and non-randomized clinical trial	38 partially remitted BD/UD and 18 HC. BD/UD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Recollection memory process dissociation task	Performance: poorer in BD/UD. Activity: BD/UD ⬇ recollection-specific activation in anterior parahippocampal gyrus.
Jamadar *et al* (2013)[62]	Case-control study	32 BD (phase not specified) and 133 HC (and 74 SZ). BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Semantic object retrieval task	Performance: poorer in BD. Activity: BD ⬇ retrieval-specific inferior parietal lobule.
Kelley *et al* (2013)[66]	Case-control study	16 depressed, psychotic UD, 15 depressed, nonpsychotic UD, and 16 HC. 68% of UD medicated (antidepressants, mood stabilizers, antipsychotics and/or benzodiazepines)	Verbal declarative memory task	Performance: only poorer in psychotic UD (> < HC and non-psychotic UD). Activity: all UD ⬇ right ACC activity during encoding and retrieval. Psychotic UD ⬇ encoding-related hippocampus, insula, and middle frontal gyrus activity and ⬆ retrieval-related PFC and parietal activation > < HC and nonpsychotic UD.
Oertel-Knöchel *et al* (2013)[79]	Case-control study	26 remitted BD 1 and 25 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Verbal learning and recognition test	Performance: poorer in BD. Activity: BD ⬇ encoding-related activity in left middle and superior frontal gyrus. BD ⬇ retrieval-related activity in middle and inferior frontal gyrus, precuneus, cuneus, parahippocampal gyrus and the posterior cingulate, and in the caudate nucleus.
Attention				
Smucny *et al* (2017)[95]	Case-control (3 sample design)	24 BD 1 with psychotic features (phase not specified) and 53 HC (and 70 SZ). BD medicated (mood stabilizers and/or antipsychotics)	AX-continuous performance task	Performance: trend-level impairment in BD. Activity: combined BD and SZ group ⬇ dlPFC and superior parietal response (no difference between SZ and BD) and BD also ⬇ ACC activity (> < HC).
Fleck *et al* (2012)[49]	Case-control study	50 manic/mixed BD 1 and 34 HC. BD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Continuous performance task	Performance: BD: poorer sustained performance. Activity: BD ⬆ bilateral amygdala activation and ⬇ activity over time in dorsal and ventral regions of an anterior-limbic network and in left striatum thalamus.
Strakowski *et al* (2004)[98]	Case-control study	10 euthymic unmedicated BD and 10 HC.	Continuous performance task	Performance: no difference. Activity: BD ⬇ activity in medial frontal cortex and fusiform gyrus and ⬆ inferior frontal cortex and vlPFC regions and limbic regions, insula, postcentral, occipito-temporal, and parietal cortex.
Korgaonkar *et al* (2013)[68]	Case-control study	30 depressed UD and 30 HC. UD antidepressant-naïve.	Continuous performance task	Performance: poorer in UD. Activity: UD ⬆ ACC activity and ⬇ right dlPFC activity.
Desseilles *et al* (2011)[44]	Case-control study	14 depressed UD and 14 HC. UD unmedicated	Detection task	Performance: no difference. Activity: Aberrant effective connectivity, with decreased parietal top-down modulation of early occipital processing of visual stimuli.
Desseilles *et al* (2009)[43]	Case-control study	14 depressed UD and 14 HC. UD unmedicated	Detection task	Performance: poorer in UD in high-load conditions. Activity: UD ⬆ subgenual cingulate/medial orbitofrontal cortex activity and ⬇ functional connectivity between fronto-parietal networks and visual cortices. UD: lack of load-related increased coupling between parietal or frontal regions and visual cortices.
Korgaonkar *et al* (2013)[68]	Case-control study	30 depressed UD and 30 HC. UD antidepressant-naïve.	Oddball task	Performance: poorer in UD. Activity: No difference in prefrontal activity.
Implicit learning				
Naismith *et al* (2010)[77]	Case-control study	19 depressed UD and 20 HC. 89% of UD medicated (antidepressants, mood stabilizers, antipsychotics, and/or benzodiazepines)	Motor sequencing implicit learning task	Performance: UD impaired implicit learning. Activity: UD ⬇ dlPFC and ⬆ superior temporal gyrus and cerebellum activity.

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TABLE 3. Continued

Author	Study design	Participants	fMRI paradigm	Findings
Genzel *et al* (2015)[53]	Case-control (3 sample design)	16 depressed UD and 16 HC (and 16 SZ). UD medicated (antidepressants, antipsychotics, and/or benzodiazepines)	Sequential finger-tapping task	Performance: UD impaired implicit learning. Activity: UD ⬇ task-induced deactivation of DMN and ⬇ hippocampus-PFC connectivity during the task performance. After one night of memory consolidation: UD failed to show normal overnight ⬇ activation of basal ganglia and PFC.

Abbreviations: HC: Healthy control, BD: Bipolar disorder, UD: Unipolar disorder, SZ: Schizophrenia, PFC: prefrontal cortex, dlPFC: dorsolateral PFC, vlPFC: ventrolateral PFC, ACC: Anterior cingulate cortex, sig. diff: Significant difference, >< : Compared to.

displayed *hyper*-activity in dorsal and rostral ACC activation,[68,92,106,107] although 1 study observed ACC *hypo*-activation.[120] As in BD, UD patients also showed altered FC within the ACC and between ACC and parietal and temporal hubs.[93,100] Finally, a study investigating both UD and BD in depressed or remitted states in comparison with HC reported more pronounced executive deficits in BD than in UD, which were coupled with *hypo*-activity in BD and *hyper*-activity in UD.[92]

Learning and memory

Fifteen studies investigated learning and memory: 5 in BD,[54,58,62,79,80] 9 in UD,[13,46,47,65,66,76,102,103,111] and 1 in both[24] (see Table 3).

Learning and memory in bipolar disorder. Three (60%) studies of remitted BD patients found impaired performance across verbal and nonverbal memory tasks,[62,79,80] while the remaining 2 (40%) studies of associative learning reported no performance deficits.[54,58] Bipolar disorder patients generally exhibited encoding-related *hypo*-activation in a network of inferior and middle frontal gyrus, ACC, dlPFC, superior parietal lobule, and insula regions in 80% of studies, independent of recall performance,[54,58,79,80] or a combination of *hypo*-activation within nodes of this fronto-parietal network and dlPFC *hyper*-activity.[54] During memory retrieval, remitted BD patients also showed primarily *hypo*-activation in the middle and inferior frontal gyrus and dlPFC,[54,79] as well as of the hippocampus and parahippocampal gyrus.[24,54,79,80] Finally, one study also found less retrieval-related deactivation of DMN regions including the temporo-parietal junction.[80]

Learning and memory in unipolar disorder. In UD, 5 (56%) studies found no differences on memory performance between HC and symptomatic or remitted UD.[46,47,102,103,111] The last four (44%) studies reported memory impairment in symptomatic (with and without psychotic features) and remitted patients.[13,65,66,76]

Encoding-related hippocampal and parahippocampal *hypo*-activation were observed in some studies of UD patients with recall deficits.[13,65,66] Moreover, studies showing no behavioral differences generally failed to demonstrate any encoding- and retrieval-related hippocampal hypo-activity.[46,102,103,111] Another consistent finding in UD patients was the absence of a "normal" association between greater hippocampal and parahippocampal activity during encoding and more subsequent retrieval success.[13,46] Another common finding was that patients with poorer memory performance showed encoding-related *hypo*-activation in the middle and medial frontal gyrus and ACC.[13,65,66] During memory retrieval, patients were found in several studies to *hyper*-activate prefrontal structures including the inferior frontal gyrus[13,66,102,103] and *hypo*-activate the hippocampus and parahippocampal gyrus.[24,65,76]

Attention

Six studies examined the neural basis of attention: 3 in BD[49,95,98] and 3 in UD.[43,44,68]

Attention in bipolar disorder. The 3 fMRI studies of manic and remitted BD patients focused on sustained attention, for which performance was impaired in 2 studies[49,95] and comparable to HC in one study.[98] Regardless of performance, BD patients exhibited replicated *hyper*-activation in limbic structures including the amygdala.[49,98] Additionally, patients with performance impairments exhibited *hypo*-activation of cognitive control regions including the dlPFC, vlPFC, and parietal cortex.[49,95] In contrast, cognitively intact patients exhibited *hyper*-activation of the inferior frontal cortex, vlPFC, insula, and parietal regions.[98]

Attention in unipolar disorder. The 3 fMRI studies in symptomatic UD reported reduced sustained and selective attention performance, respectively.[43,44,68] Two of

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these studies found that this deficit was accompanied by aberrant FC between fronto-parietal regions and occipital visual areas, resulting in decreased top-down modulation of early occipital processing.[43,44] Korgaonkar *et al*[68] also observed dlPFC *hypo*-activity during sustained attention. In contrast, no abnormal dlPFC activation was detected during a selective attention test despite impaired task performance.[68] However, the study involved only region of interest (ROI) analysis, focusing on the dlPFC and dmPFC, and potential abnormalities in other cognitive control regions were thus not assessed.

Implicit learning

Two studies of symptomatic UD investigated implicit learning using a motor sequencing implicit learning task and a sequential finger-tapping task, respectively.[53,77] Both found impaired implicit learning in patients, which was accompanied by dlPFC *hypo*-activity and impaired deactivation of the DMN. Patients also exhibited decreased FC between the hippocampus and PFC.[53] In addition, one night of memory consolidation did not result in the "normal" reduction in task-related PFC and basal ganglia activation in UD patients. This could indicate disruption of the brain processes underlying implicit memory consolidation and thus less automation of responses in UD.

Interim summary of cognitive impairment studies

Taken together, the most consistent neural activity changes during working memory, executive skills, memory, and attention domains across BD and UD were abnormal activation of dlPFC, frontopolar, and parietal regions coupled with failure to deactivate the DMN. Patients with BD generally exhibited PFC *hypo*-activation independent of performance levels, while UD patients generally displayed PFC *hypo*-activation of these structures when performance was impaired and *hyper*-activity in this region when performance was preserved. Another common marker of learning difficulties in mood disorders was encoding-related *hypo*-activation of middle frontal gyrus and ACC. A common phenomenon across the cognitive domains and diagnoses was also the abnormal FC within the PFC regions including the ACC and between PFC and subcortical/parietal regions. In contrast, hippocampal and parahippocampal *hypo*-activity was shown primarily during memory retrieval in BD and was not consistently observed in patients with UD. Instead, UD patients tended to lack the "normal" correlation between hippocampal engagement during encoding and subsequent retrieval success. Taken together, aberrant (hypo- and hyper-) activity (depending on the level of cognitive performance) in fronto-parietal cognitive control regions and failure to deactivate the DMN may thus represent common fMRI biomarkers of cognitive impairments in mood disorders.

Cognitive improvement

Nine fMRI studies investigated the neural correlates of *cognitive improvement* in mood disorders, of which 5 focused on *specific* mood-independent cognitive improvement in response to candidate cognition treatments,[22–25,123] and 4 investigated *nonspecific* cognitive improvement following symptom reduction[106,124–126] (see Table 4).

Specific treatment-related cognitive improvement

The 5 studies that investigated specific treatment-related cognitive improvement focused on the effect of 3 different drug treatments [erythropoietin (EPO),[22,23] lamotrigine,[123] vortioxetine[25]] and one psychological intervention, cognitive remediation (CR) therapy.[24] The treatment-associated changes were investigated on working memory in 4 studies and on learning and memory in 2 studies.

Working memory. Consistent findings regarding the neural correlates of treatment-related improvement of working memory were modulation of task-related activity in the cognitive control regions including the dlPFC and superior frontal gyrus[23–25,123] and suppression of activity in DMN regions like the hippocampus.[23,25] Specifically, Miskowiak *et al*[23] showed in a randomized placebo-controlled controlled trial (RCT) that 8 weeks of treatment with erythropoietin (EPO) increased working memory capacity in UD and BD, which was accompanied by—*and correlated with*—enhanced task-related activity in the right superior frontal gyrus and deactivation of the left hippocampus. Similarly, Meusel *et al*[24] found in an open-label uncontrolled study that CR therapy increased task-related activity in lateral PFC, medial frontal gyrus, superior temporal, and lateral parietal regions. As in the EPO trials, CR-related frontal and parietal activity increase correlated with improved working memory performance. It should be noted, however, that the CR-related working memory improvements did not reach statistical significance, and practice effects could not be excluded given the absence of a control group. The findings regarding the neural correlates of CR should therefore be interpreted with caution.

In contrast to the above-mentioned studies, Smith *et al*[25] found that 2 weeks of treatment with the monoaminergic antidepressant vortioxetine *reduced* working memory–related dlPFC activity in remitted UD in the absence of changes in working memory performance. Notably, these patients displayed no objective impairment in working memory performance in

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TABLE 4. Studies of the neural underpinnings of cognitive improvement

Author	Study design	Participants	Treatment	Duration	Test times	fMRI paradigm (cognitive domain)	Symptom change	Findings
Neural correlates of specific treatment-related cognitive improvement								
Miskowiak *et al* (2016)[22]	Randomized, double-blind, placebo-controlled, parallel-group design	28 moderately depressed TRD (14 EPO) and 34 partially remitted BD (18 EPO) on antidepressant/mood stabilizing medication.	EPO >< Saline	8 weeks	Baseline and week 14	Explicit picture encoding task (learning and memory)	EPO did not affect mood	Performance: EPO ⬇ picture recall >< saline. Activity: EPO ⬆encoding-related bilateral dlPFC and left-side temporo-parietal response >< saline but did not affect encoding-related hippocampal activity. Change in neural activity correlated with improvement of recall performance.
Meusel *et al* (2013)[24]	Open-label, noncontrolled design	28 partially remitted BD/UD with concomitant treatment and 18 HC	Cognitive remediation	10 weeks	Baseline and week 10	Adapted recollection memory process dissociation task (learning and memory)	CR had no effect on mood	Performance: CR did not improve performance. Activity: CR ⬆ recollection-related activation of right and left hippocampus. Changes in hippocampal activity correlated with improvements in memory performance.
Haldane *et al* (2008)[123]	Open-label, noncontrolled design	12 stable BD 1 with no concomitant treatment (8 in final analysis)	Lamotrigine	12 weeks	Baseline and 12 weeks	N-back task (working memory)	Lamotrigine did not affect mood	Performance: No effect of lamotrigine. Activity: Lamotrigine ⬆ activation in the superior frontal, cingulate gyri, and left medial frontal gyrus.
Smith *et al* (2017)[25]	Randomized, double-blind, placebo-controlled, parallel-group design	48 remitted UD with no concomitant treatment and 48 HC	Vortioxetine >< placebo	2 weeks	Baseline and 2 weeks (day 12–14)	N-back task (working memory)	Vortioxetine improved self-rated mood	Performance: no effect of vortioxetine >< placebo. Activity: vortioxetine ⬇ WM-related activation in right dlPFC, left hippocampus, left thalamus and right insular cortex). After adjustment in self-rated mood, vortioxetine additionally ⬇ response in right insula, fusiform gyrus, and lingual gyri.
Miskowiak *et al* (2016)[23]	Randomized, double-blind, placebo-controlled, parallel-group design	24 moderately depressed TRD (14 EPO) and 32 partially remitted BD (16 EPO) with concomitant treatment	EPO >< Saline	8 weeks	Baseline and week 14	N-back task (working memory)	EPO did not affect mood	Performance: EPO ⬆ WM performance accuracy >< saline. Activity: EPO ⬆ right SFG and ⬇ left hippocampal activity (region of the DMN) >< saline. Changes in neural activity correlated with improvement of performance.
Meusel *et al* (2013)[24]	Open-label, noncontrolled design	23 partially remitted BD/UD with concomitant treatment and 15 HC	Cognitive remediation	10 weeks	Baseline and week 10	N-back task (working memory)	CR had no effect on mood	Performance: CR did not improve performance. Activity: CR ⬆ right and left lPFC, right medial frontal, superior temporal, and lateral parietal regions. Activation changes in frontal and parietal regions correlated with changes in performance.
Neural correlates of nonspecific cognitive improvement following								

symptomatic improvement								
Wagner *et al* (2010)[106]	Prospective, naturalistic open-label, nonrandomized controlled design	20 depressed UD with concomitant treatment (only benzodiazepines) and 20 HC	Citalopram (12) >< reboxetine (8)	6 weeks	Baseline and 6 weeks	Color-word Stroop task (Executive skills)	HDRS scores: Reboxetine: 24 ± 5 → 9 ± 6; Citalopram: 2 ± 4 → 8 ± 6	Performance: no difference before or after treatment. Activity: no difference between UD groups and HC in relative hyper- or hypo-activity after treatment (UD showed hyper-activation in fronto-parieto-temporal network and rostral ACC before treatment). Main effect of time for all UD: ⬇ activity in left middle temporal lobe, right inferior parietal lobule, right ventrolateral prefrontal cortex and bilaterally in superior parietal lobe. Citalopram ⬇ activity in right amygdala–hippocampus complex.
Kaladjian *et al* (2009)[124]	Case-control follow-up study	10 manic BD and 10 HC.	Mood stabilizers, antipsychotics, or both	143 days ±94	Baseline and follow-up	Go/no-go task (executive skills)	Manic → remission	Performance: ⬆ from time 1 to time 2. Activity: left amygdala the only brain region to show a differential activation change over time between BD and HC. BD ⬇ activation in left amygdala at T2 >< T1.
Walsh *et al* (2007)[125]	Open-label, noncontrolled design	20 depressed UD with no concomitant treatment and 20 HC	Fluoxetine hydrochloride	8 weeks	Baseline and week 2 and 8	N-back task (working memory)	HDRS scores: 21 ± 2 → 9 ± 6	Performance: No effect of treatment (UD slower than HC). Activity: Normalization of quadratic load-response in caudate nucleus and thalamus in UD.
Sankar *et al* (2017)[126]	Open-label, noncontrolled design	23 depressed UD with no concomitant treatment and 22 HC	Duloxetine	12 weeks	Baseline, weeks 1, 8, and 12	Delayed match-to-sample/Sternberg task (working memory)	HDRS scores: 22 ± 3 → 7 ± 5	Performance: No effect of treatment (similar performance in UD and HC). Activity: ⬇ encoding-related right precentral gyrus and left middle temporal gyrus activity, ⬇ maintenance-related left inferior temporal activity, ⬇ retrieval-related left inferior parietal activity, and ⬇ delayed retrieval-related right precentral and cerebellum activity.

Abbreviations: EPO: Erythropoietin, TRD: Treatment resistant depression, HC: Healthy control, BD: Bipolar disorder, UD: Unipolar disorder, PFC: prefrontal cortex, dlPFC: dorsolateral PFC, lPFC: lateral PFC, SFG: superior frontal gyrus, rACC: Rostral anterior cingulate cortex, WM: Working memory, HDRS: Hamilton depression rating scale, YMRS: Young mania rating scale, BDI: Beck's depression inventory, SD: Standard deviation, T1: First time point, T2: Second time point, >< : Compared to.

comparison with HC despite subjective cognitive complaints.[25] The reduced dlPFC activity in vortioxetine treated individuals was interpreted as increased cortical efficiency given the absence of overt change in these (cognitively intact) patients' working memory performance. Indeed, the previously noted distinction between *efficiency* and *capacity* is likely to explain the different direction of dlPFC change in response to vortioxetine vs. EPO treatment. Interestingly, vortioxetine also strengthened the deactivation of the hippocampus during working memory performance, similar to the effects of EPO.[23]

Finally, a small open-label, noncontrolled study of lamotrigine treatment in remitted BD patients revealed increased working memory–related activation over time in bilateral superior frontal and cingulate gyri and left medial frontal gyrus in the absence of changes in performance.[123] However, it is difficult to determine whether this represents a beneficial effect on the neural activity associated with cognitive performance given (i) that the direction of activity change was opposite to the hypothesized (reduced) activity associated with greater efficiency as seen after vortioxetine treatment, (ii) the lack of associated cognitive improvement as seen after EPO treatment, and (iii) the within-group design with no control group, which could not exclude nonspecific effects of repeated testing and learning over time.

Learning and memory. Hippocampus and dlPFC were reported to underlie treatment-related improvements in the 2 studies of learning and memory.[22,24] In the RCT by Miskowiak *et al*,[22] EPO treatment increased encoding-related bilateral dlPFC and left-sided temporo-parietal response across BD and UD patients and improved subsequent recall performance. Importantly, the EPO-associated activity increase in dorsal PFC and temporo-parietal regions correlated with improvement of recall performance across the entire cohort, suggesting that this effect was mechanistically important.[22] In contrast, no treatment-associated change in hippocampal response during memory encoding was observed.[22] This contrasts with the finding by Meusel *et al*[24] of CR-related increase in hippocampus during retrieval. However, given the within-group design with no control group in the CR trial, the hippocampal activity increase over time could reflect nonspecific effects of repeated testing rather than specific effects of the intervention.

Cognitive improvement following symptom reduction

Four studies examined improvements in working memory and executive skills following reduction in mood symptoms, of which 3 studies were conducted in depressed UD patients[106,125,126] and one in manic BD patients.[124]

In general, cognitive improvement following symptom reduction was associated with *decreased* activation both within cognitive control and DMN regions.[106,124,126] Indeed, Kaladjian *et al*[124] found that improved cognitive performance in BD patients after transition from a manic to a remitted state was accompanied by decrease in left amygdala activation during an inhibitory control task. Similarly, Wagner *et al*[106] found that reduction in depressive symptoms in UD patients after successful citalopram treatment was accompanied by decreased activity in the amygdala–hippocampus complex during color-word Stroop performance. Successful citalopram and reboxetine treatment of UD patients also attenuated pre-treatment *hyper*-activation of the fronto-parieto-temporal network and rostral ACC during a cognitive control task.[106] In contrast, task-related caudate nucleus and thalamus activity increase has also been observed in UD patients after reduction in depressive symptoms.[125]

Interim summary of cognitive improvement studies

Different pharmacological and psychological treatments that *directly* target cognition seem to specifically modulate dorsal PFC activity—with the direction of this activity change depending on the associated changes in performance levels—and to attenuate DMN hyper-activity. The observed opposite effects of EPO and vortioxetine on working memory-related dlPFC activity may be explained by the associated changes in *capacity* (ie, performance increase) or *efficiency* (with no associated behavioral change), respectively. Further, a common neural activity change observed after EPO and CR treatments was increase in task-related dlPFC activity. In contrast, encoding-related hippocampal activity was not modulated by EPO, and it is unclear whether the observed hippocampal activity increase after CR represented a treatment effect or nonspecific changes with repeated testing. Further, indirect cognitive improvement following symptom reduction was consistently accompanied by reduced limbic and DMN activity and reversal of pre-treatment fronto-parietal hyper-activity during task performance. This may represent reduced interference from hyper-active *task-negative* (limbic and DMN) regions after attenuation of mood symptoms and, consequently, less need for compensatory over-activation in cognition relevant regions.

Discussion

This systematic review examined the most consistent neural correlates for cognitive *impairments* and cognitive *improvement* in mood disorders to identify putative neurocircuitry-based targets for novel cognition treatments. We identified a total of 100 studies of the

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neuronal underpinnings of working memory, executive skills, learning and memory, attention, and implicit learning, respectively, and 9 studies of the neuronal changes associated with cognitive improvements. The most consistent findings regarding neural correlates for cognitive impairments across domains and diagnoses were aberrant (*hypo-* or *hyper-*) activity in medial and dorsal PFC cognitive control regions and parietal cortex, with the *direction* of this aberrant activity depending on cognitive performance levels as well as *hyper*-activity in the DMN and limbic regions. Candidate treatments that *directly* targeted cognition seemed to (i) specifically modulate dorsal PFC and temporo-parietal activity, with the *direction* of the activity change depending on whether it was accompanied by improved cognitive performance, and (ii) attenuate DMN hyper-activity. In contrast, *indirect* cognitive improvements following symptom reduction were commonly accompanied by attenuation of limbic hyper-reactivity coupled with reversal of pre-treatment fronto-parietal *hyper*-activity during cognitive performance.

Putative biological targets for pro-cognitive treatments

Remarkably, a few *common* brain regions were consistently identified as showing abnormal activity in UD and BD across a variety of fMRI paradigms tapping into different cognitive domains. Specifically, fMRI studies of working memory, executive skills, memory encoding, and sustained attention revealed reliable evidence for aberrant (predominantly *hypo-*) activity in dorsal PFC and fronto-polar regions as well as abnormal FC within the PFC and between the PFC, parietal, and limbic regions. Notably, the dorsal and lateral areas of the PFC are involved in a variety of "top-down" control processes that may be important across several cognitive domains, including active working memory maintenance and manipulation, attention control and -switching, impulse inhibition, and strategic encoding.[19] This may explain the association between aberrant activity in these regions and impaired performance across diverse neurocognitive tests. Another consistent finding across fMRI studies of working memory, executive skills, and attention was reduced deactivation of the DMN and limbic structures during active task performance. This is in line with the hypothesis that cognitive impairments in mood disorders may exacerbated by a failure to suppress task-irrelevant neural activity associated with emotional reactivity, self-focus, and rumination.[14,21] While abnormal hippocampal activity during memory retrieval was a reliable finding in BD patients,[24,54,79,80] it was not consistently observed in UD patients.[46,102,103,111] However, several studies found that UD patients failed to display the "normal" correlation between encoding-related hippocampal activation and subsequent retrieval success. This points to dysregulated encoding-related recruitment of the hippocampus rather than hippocampal hypo- or hyper-activity *per se*. Taken together, abnormal (predominantly *hypo-*) activity in dorsal and lateral PFC, aberrant PFC FC, and failure to suppress DMN activity emerged as the most consistent neural correlates of cognitive impairments across UD and BD and therefore represent the most promising biological targets for pro-cognitive interventions.

Efficiency vs. capacity: the importance of performance levels

The discrepant findings regarding the direction of abnormal task-related activity in dorsal PFC (particularly in UD) and of the dorsal PFC activity change in response to pro-cognitive interventions[22,23,25] are best explained in relation to patients' levels of cognitive performance. Specifically, dorsal PFC *hyper*-activity has been proposed to reflect *reduced cortical efficiency*, that is, the need for recruitment of more neural resources to maintain normal performance,[127] whereas dorsal PFC *hypo*-activity is accompanied by *reduced cognitive capacity*, that is, performance decline when the task load exceeds individuals' cognitive capacity.[127]. Callicott *et al*[127] proposed that the dorsal PFC *hyper-* and *hypo*-activity in patients can be explained by a leftward shift in the generally observed inverted U-shaped response curve between the cognitive task load and dorsal PFC activity. Specifically, neuropsychiatric patients may reach the peak BOLD response faster (ie, at a lower cognitive load) than HC, after which their dorsal PFC activity and associated performance success go down when the task load exceeds patients' cognitive capacity[127] (for illustration, see our revised model based on Callicott *et al*[127] in Figure 2). Indeed, we observed consistent evidence in this systematic review for dorsal PFC *hypo*-activity across BD and UD patients who showed *impaired* cognitive performance in comparison with HC, whereas patients who maintained normal performance levels were commonly characterized by dorsal PFC *hyper*-activity. Also consistent with this model is the suggestion that frontopolar *hypo*-activation in BD results from the cognitive load exceeding patients' capacity to activate this region, which leads to deterioration of their task performance.[63] Further, co-variation for performance levels in another study resulted in frontopolar *hyper-* (rather than *hypo-*) activation in BD.[29] Nevertheless, 2 studies failed to show such an association between hypo-activity and reduced cognitive capacity; instead they found dorsal PFC *hyper*-activation in patients with executive dysfunction.[48,92] Given this, task-related PFC *hyper*-activity may also result from *unsuccessful* attempts to maintain normal task performance.

Consistent with the notion that abnormal dorsal PFC and DMN activity may be common biological targets for cognition treatments, the identified cognition trials

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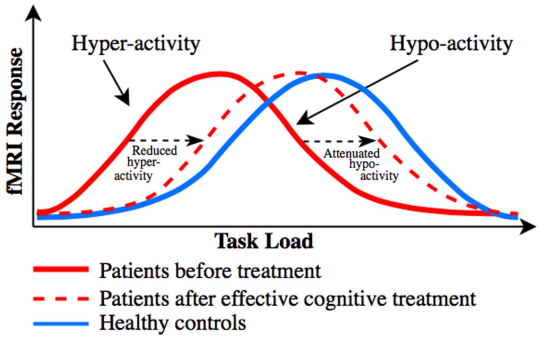

FIGURE 2. Putative distinct load-response curves, which may unify the discrepant findings regarding dorsal PFC activity change associated with cognitive impairment and cognitive improvement in mood disorders. Model revised from Callicott *et al.*[127] Distinct inverted curves for the association between task load (task difficulty) and dorsal PFC activity in patients with neuropsychiatric disorders (red solid curve) and healthy controls (blue solid curve), and distinct changes in task-related dorsal PFC activity in response to treatments targeting cognition. Patients tend to display dorsal PFC *hyper*-activity in comparison with healthy controls when performance is maintained at medium task loads and dorsal PFC *hypo*-activity when performance declines at higher loads (where the task demand exceeds patients' cognitive capacity). We hypothesize that pro-cognitive treatments of patients shift the bell-shaped curve toward the right (ie, toward "normality"), as indicated with the red dotted curve. Depending on the cognitive task load and hence patients' performance levels, this rightward shift will be reflected by either (A) reduction in pre-treatment dorsal PFC *hyper*-activity in (cognitively intact) patients who display no treatment-related change in performance (ie, increased cortical *efficiency*), such as seen after vortioxetine treatment,[25] or (B) attenuation of pre-treatment dorsal PFC hypo-activity (ie, *enhanced* dorsal PFC response) in cognitively impaired patients who display treatment-related cognitive improvement (ie, enhanced cognitive *capacity*), as seen after erythropoietin[22,23] and cognitive remediation treatments.[24]

revealed common treatment-related modulation of activity in these networks. In particular, EPO and CR increased task-related dorsal PFC and parietal activity, which correlated with increased recall performance. Further, modulation of working memory associated dlPFC activity was a common neural correlate of EPO and vortioxetine treatments, although the *direction* of this change differed between the interventions. We hypothesize that the apparent discrepancy regarding the direction of the dorsal PFC change can be explained by a common treatment-related *rightward shift toward "normality"* in the putative bell-shaped response curve between task load and dorsal PFC response[127] (for illustration, see Figure 2). Depending on the cognitive task load and hence patients' performance levels, this rightward shift will be reflected by either (A) reduction in pre-treatment dorsal PFC *hyper*-activity in (cognitively intact) patients who display no treatment-related change in performance (ie, increased cortical *efficiency*), such as seen after vortioxetine treatment,[25] or (B) attenuation of pre-treatment dorsal PFC hypo-activity (ie, *enhanced* dorsal PFC response) in cognitively impaired patients who display treatment-related cognitive improvement (ie, enhanced cognitive *capacity*), as seen after EPO[22,23] and CR treatments[24] (see Figure 2).

Remarkably, meta-analytical findings point to similar increase in task-related dlPFC and medial PFC activity as the most robust markers of cognitive improvements following CR treatments in schizophrenia.[128] In contrast, CR-related activity change in *other* cognition-relevant regions, such as the hippocampus, was less consistent across schizophrenia trials.[128] This is consistent with the lack of reliable treatment effects on encoding-related hippocampal activity in mood disorders. Together, these findings point to modulation of dorsal PFC and the DMN as the most promising surrogate marker of pro-cognitive effects of both *pharmacological* and *cognitive* treatments across several neuropsychiatric disorders.

Studies of *indirect* cognitive improvement following reduction in mood symptoms yielded a somewhat different pattern of neural changes: decrease in *hyper*-activity in limbic and DMN coupled with reversal of pre-treatment fronto-parietal hyper-activity. Such indirect cognitive improvement could thus be mediated primarily by decreased interference from limbic and DMN hyper-reactivity in parallel with patients' symptom reduction and consequent "relaxation" of the compensatory hyper-activity in cognitive control regions.

Methodological challenges and opportunities

A greater proportion of studies in UD than in BD patients displayed performance deficits on fMRI paradigms tapping into executive function, which contrasts with evidence for greater severity of cognitive deficits in BD.[129] A likely explanation is that fMRI paradigms are generally not optimized for detection of deficits in cognitive performance but for detection of *compensatory neural responses* associated with intact cognitive performance.[130] Nevertheless, the differential difficulty levels of the employed fMRI paradigms, together with patients' cognitive heterogeneity, may explain the common fronto-parietal *hyper*-activity in patients with intact cognitive performance and *hypo*-activity in those with compromised performance.

Functional MRI can provide a valuable *dynamic* measure of the treatment effects at a *systems level* in the brain, which may have better predictive validity than animal models. However, there are some fundamental limitations of the fMRI technique that must be considered in relation to its implementation in treatment development strategies targeting cognition. First, the reproducibility of the BOLD fMRI response is uncertain given inconsistent test–retest reliability across different assessment times in the same individuals.[131] This limits the statistical power for detection of a treatment effect in

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fMRI studies with a repeated-measures design. Secondly, the fMRI BOLD response provides only an *indirect* measure of neural activity. This may be problematic for demonstrating neurocircuitry "target engagement" in response to treatments that influence global cerebral hemodynamic responses.[131] Indeed, this turned out to be a problem in the EPO studies, since long-term EPO administration upregulates the level of red blood cells. Nevertheless, the problem was tackled by (i) postponing the post-treatment fMRI scan until the red blood cell counts had normalized (and verifying this with blood tests), and (ii) inclusion of a visual stimulation control task with no cognitive demands to examine whether there were any potential global (cognition-unrelated) differences in neural activity between EPO and saline groups.[22,23] The golden standard approach would be to apply arterial spin labeling, which is an even more rigorous measure, to quantify and adjust for any potential physiological effects on global hemodynamic responses. Nevertheless, it may be argued that the fMRI BOLD response cannot provide a robust, reliable marker of treatment efficacy because the understanding of its biological basis is incomplete. Indeed, there is a lack of consensus in the field on whether treatment-related *increase* or *decrease* in fMRI BOLD is a marker of cognitive improvement. We propose a model that may explain these discrepant findings and become useful for interpretation of neuroimaging findings in future cognition trials (Figure 2). Specifically, the model involves consideration not only of the treatment-related change in dorsal PFC activity but also of the accompanying change in cognitive performance (or lack thereof) for the interpretation of the observed effects. Hence, assessment of treatment-related change in fMRI BOLD signal within key neurocircuitries together with change in cognition is a promising strategy for determining the *functional relevance* of any neural activity changes.

Conclusion

In conclusion, the most consistent neural underpinnings of cognitive impairments across cognitive domains and diagnoses were aberrant activity in the medial and dorsal PFC cognitive control regions and parietal cortex, with the *direction* of the aberrant activity depending on patients' cognitive performance levels. Another common finding was the failure to suppress DMN and limbic activity during cognitive performance. The findings from the cognition trials indicated that the most consistent biological targets for treatments with *direct* efficacy on cognition are (i) enhancement of activity in dorsal PFC cognitive control regions in patients with impaired cognitive performance (ie, increased capacity) or reduction of neural activity in these regions in patients with intact performance (ie, increased efficiency) (findings that may be reconciled with our proposed model for a *rightward shift* in the putative bell-shaped curve for the association between BOLD fMRI response and cognitive load; Figure 2), as well as (ii) *suppression* of activity in the DMN during cognitive performance. In contrast, indirect cognitive improvement following symptom reduction seemed to be mediated by decrease in limbic reactivity coupled with attenuation of fronto-parietal *hyper*-activity during cognitive performance. This review and integration of the findings in the field provide a first step toward a more unified understanding of the shared neural correlates of cognitive deficits in mood disorders and of treatment-associated cognitive improvements. These insights can provide a platform for studies assessing the predictive validity and reliability of treatment-related modulation of the dorsal PFC and DMN as surrogate markers for pro-cognitive effects. The perspective is the identification of a neurocircuitry biomarker model for pro-cognitive effects that can become a key tool to inform go/no-go decisions before the conduct of large-scale clinical efficacy trials in future treatment development programs.

Disclosures

Kamilla Miskowiak reports having received consultancy fees from Lundbeck and Allergan within the past 36 months.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1092852918001062

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