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Behavioral Activation and Brain Network Changes in Depression

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Behavioral activation (BA) is a well-established method of evidence-based treatment for depression. There are clear links between the neural mechanisms underlying reward processing and BA treatment for depressive symptoms, including anhedonia; however, integrated interpretations of these two domains are lacking. Here we examine brain imaging studies involving BA treatments to investigate how changes in brain networks, including the reward networks, mediate the therapeutic effects of BA, and whether brain circuits are predictors of BA treatment responses. Increased activation of the prefrontal and subcortical regions associated with reward processing has been reported after BA treatment. Activation of these regions improves anhedonia. Conversely, some studies have found decreased activation of prefrontal regions after BA treatment in response to cognitive control stimuli in sad contexts, which indicates that the therapeutic mechanism of BA may involve disengagement from negative or sad contexts. Furthermore, the decrease in resting-state functional connectivity of the default-mode network after BA treatment appears to facilitate the ability to counteract depressive rumination, thereby promoting enjoyable and valuable activities. Conflicting results suggest that an intact neural response to rewards or defective reward functioning is predictive of the efficacy of BA treatments. Increasing the benefits of BA treatments requires identification of the unique individual characteristics determining which of these conflicting findings are relevant for the personalized treatment of each individual with depression.

Keywords depression; cognitive behavioral therapy; psychotherapy; functional magnetic resonance imaging; neuroimaging.

INTRODUCTION

Behavioral activation (BA) is a structured and brief psychotherapeutic approach that aims to 1) increase engagement in adaptive activities (which are often associated with the experience of pleasure or mastery), 2) decrease engagement in activities that maintain depression or increase the risk of depression, and 3) solve problems that restrict access to rewards or maintain or increase aversive control.[1] Several studies, which include large-scale randomized controlled trials (RCTs), have investigated the efficacy of BA treatments for depression,[2-6] and meta-analyses of the cumulative findings have found moderate-to-large effect sizes for BA treatments.[7-11] Several guidelines based on the accumulating research have given BA a high status in the treatment of depression; for example, the American Psychological Association (APA) guidelines designate BA as a "well-established, validated treatment for depression."

The increasing amount of clinical evidence for the efficacy of several psychotherapy approaches and the advances in basic and translational neuroscientific research have recently led to a greater focus on neurobiological mechanisms with the aim of elucidating the mech-

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anisms of action underlying both diseases and treatments. Research on the mechanisms underlying changes in brain networks is pivotal for the development and refinement of psychological treatments,[12] because identifying these mechanisms will improve the understanding of which treatment components are causally associated with symptom improvement and will allow treatments to be refined. In particular, cognitive behavioral therapy (CBT) for depression has been the focus of various functional magnetic resonance imaging (fMRI) studies, which have identified the neurobiological mechanisms underlying treatment effects by examining changes in brain networks during CBT, and have aided in predicting the therapeutic response and prognosis of individual patients with depression by studying the activity in specific brain regions and networks.[13-19] However, unlike for CBT, insufficient research has been conducted on the neurobiological mechanisms of BA at the brain network level. Although many fMRI studies have included BA as one of the therapeutic components, such comparative studies cannot replace investigations of the independent neurobiological effects of BA alone. Despite the strong empirical support for the efficacy of BA treatment, the understanding of the mechanisms of change that lead to symptom improvement remains inadequate.

Symptoms of major depressive disorder (MDD), such as decreases in motivation, activity levels, and ability to experience pleasure, have been linked to dysfunction of the systems governing the behavioral responsiveness to positive stimuli (i.e., reward function).[20] Considering that the primary goal of BA is to increase the degree to which an individual engages in rewarding activities, BA treatment for depression is probably highly relevant to the activity of the brain's reward system. Considering the etiology and treatment mechanisms of depression, there are clear links between BA treatments for depression and the neural mechanisms involved in reward function. Despite this strong connection, the body of research on the efficacy of BA treatments has mostly evolved independently of basic and translational neuroscience studies of the biobehavioral mechanisms underlying reward functioning.[21]

Therefore, this review comprehensively examines the clinical literature describing brain network changes following BA treatments, with a particular focus on changes in BA treatment mechanisms at the brain network level, especially those related to reward function/processing, as well as exploring whether functional neuroimaging markers can predict BA treatment outcomes. The aim in writing this review was to enhance our understanding of the therapeutic mechanisms of BA in the treatment of depression and thereby improve the ability to provide personalized treatments based on the underlying neural circuits.

BA IN DEPRESSION AND EMPIRICAL EVIDENCE

Brief history of BA

BA is rooted in behaviorism.[22-24] The first wave of behaviorism involved the behavioral model of depression, which was based on the premise that depression occurs after losing a major source of positive reinforcement. However, further developments of the behavioral model were overshadowed during the 1960s by a second wave of psychotherapy, called the "cognitive revolution." Beck and colleagues recognized the value of behavioral techniques and incorporated behavioral therapy strategies into cognitive therapy (CT),[25] and interest in behavioral treatments for depression resurfaced during the 1990s and 2000s. This included Jacobson et al.[26] comparing treatment effects in 150 adult patients with MDD randomized to receiving a BA component; to receiving a BA component plus strategies designed to restructure automatic thoughts; and to receiving the full CT package, including BA. They found that the outcomes in the BA-only group were equivalent to those under the other two conditions,[26,27] which rekindled interest in behavior-based approaches to depression treatment and BA as a stand-alone intervention.[28-30] Emphasis was placed on the functional analysis of contextual factors and behavior in depression assessments and interventions, or functional contextualism, as described by Hayes et al.[31] Therefore, rather than focusing on changing or eliminating the form of a problem, psychotherapy searched for secondary changes by identifying the context in which problematic cognitions, emotions, and behaviors occur and intervening to change their function. This has led to BA becoming one of the modern third wave ("contemporary contextual") approaches to psychotherapy.

Psychological mechanism underlying BA treatments

Lewinsohn and colleagues[23,24,32] established a behavioral model of depression that was initially based on three assumptions: 1) response-contingent positive reinforcement at low levels eliciting stimuli for depressive behavior (mood and somatic feelings), 2) reduced response-contingent positive reinforcement being a sufficient explanation for depression, and 3) the total amount of response-contingent reinforcement being a function of the number of events that occur in the environment, potentially reinforcing the individual, the probability of the event occurring, and the frequency of the individual's instrumental behavior triggering the event. Furthermore, depression was believed to be preceded by a decrease in re-

sponse-contingent reinforcement and to act as a covariate with the level of this reinforcement. Low levels of reinforcement are key antecedents in depression development, with depression decreasing when positive reinforcement increases with treatment. Martell et al.[29] proposed the TRAP/TRAC (Trigger, Response, Avoidance Pattern/Trigger, Response, Alternative Coping) model to describe the contexts in which individuals with depression exhibit avoidance behaviors and BA interventions for these avoidance patterns. "Avoidance Patterns" are exhibited when an event triggers a negative response ("Trigger"), causing a loss of opportunities to solve issues or access available reinforcers. Avoidance behavior creates a feedback loop of depressed moods by missing opportunities to cope with subsequent contextual triggers. However, engaging in constructive behaviors such as "Alternative Coping" breaks the avoidance cycle and depressed moods. Thus, a reduction in avoidance coping leads to increased opportunities for engagement with sources of reward in the environment. Another previous study[33] extracted the following eight BA techniques from six BA treatment manuals: activity monitoring, contingency management, value and goal assessments, activity scheduling, procedures targeting verbal behavior, procedures targeting avoidance, skill training, and relaxation.[25,29,34-38] The psychotherapeutic components of BA are discussed in more detail by Kanter et al.[33]

Efficacy of BA treatments

A large RCT involving 241 adults with MDD compared the efficacy of BA treatments for 16 weeks in reducing depressive symptoms with those of medication (paroxetine) and CT, and with a placebo control group. The results showed that the efficacy of BA was comparable to that in pharmacotherapy in the acute treatment of MDD, and better than CT in patients with more-severe depressive symptoms.[2] A subsequent study followed up those individuals who had responded to treatment 1 year later, and found that the rate of depression relapse after medication discontinuation was lower in patients who received BA or CT, with no significant difference between BA and CT.[3] These findings suggest that BA treatment is at least as effective in improving acute depressive symptoms and preventing relapse as the existing standard of care and well-established psychotherapy strategies for depression.

A meta-analysis of BA treatments that included 16 studies involving 780 participants observed that the pooled effect size for the difference between the treatment and control groups at posttest was significant at 0.87, while in 10 of the included studies that compared BA with CT found no significant difference between the two groups, even at follow-up.[7] Another study extended that analysis[7] by including 26 RCTs involving 1,524 participants,[8] and found a large effect size of 0.74 standard mean differences (SMDs) between the BA and control groups in post-hoc analyses, and a small but significant superiority of 0.42 SMDs in the 4 studies in which BA was compared with pharmacotherapy, confirming the clinical efficacy of BA.

BA is highly regarded as an evidence-based psychotherapy strategy for the treatment of depression. The APA guidelines list BA as 1 of 12 empirically supported treatments for depression. The United Kingdom National Institute for Health and Care Excellence guideline[39] for treating depression in adults recommends that the applied treatment should be based on the depression severity, and includes BA as a first-line treatment for both severe and mild depression. The clinical guidelines for MDD treatment in adults published by the Canadian Psychiatric Association and Canadian Network for Mood and Anxiety Treatments[40] recommend BA as a first-line treatment for acute depressive symptoms, along with CBT and interpersonal therapy (IPT), and as a second-line maintenance treatment to prevent relapse. Guidelines produced by the Scottish Intercollegiate Guidelines Network[41] for non-drug treatments of adult depression recommend BA as a first-line treatment along with CBT and IPT.

Relationships between BA treatments and anhedonia in depression

It has recently been suggested that popular depression treatments such as CBT and antidepressants are less effective in treating anhedonia and low positive affect,[42] which underscores the need for a deeper understanding of the mechanisms of change underlying reward-focused treatments. New strategies are needed that target low positive affect, decreased motivation and pleasure, and anhedonia, which are primary symptoms of MDD.[20,43] Accordingly, Nagy et al.[44] proposed the transdiagnostic behavioral activation therapy for anhedonia (BATA) for restoring reward motivation and responsiveness. Clinical studies have shown that BA is associated with improvements in anhedonia. The administration of BA treatment to 33 outpatients diagnosed with MDD resulted in a significant reduction in their anhedonia symptoms.[45] Another study involving 440 patients with MDD randomized to BA or CBT demonstrated an improvement in anhedonia symptoms in both treatment groups during acute treatment, with no significant intergroup difference.[46] The efficacy of BA treatment for anhedonia has also been validated in adolescent populations.[47,48]

DYSFUNCTION OF THE REWARD-PROCESSING NETWORK AND DEPRESSION

What is the reward-processing network?

Deficits in reward processing have been proposed as a candidate mechanism underlying anhedonia, which involves a consistent lack of pleasure and interest in nearly all daily life activities.[49] fMRI studies have made significant progress over the past decade in improving the understanding of brain mechanisms underlying anhedonia and reward-processing dysfunction in MDD. Although numerous brain regions react to rewards, the cortical-basal ganglia circuit is the cardinal component of the reward system.[50] The key structures in this network are the anterior cingulate cortex, orbital prefrontal cortex (OFC), ventral striatum (i.e., the nucleus accumbens [NAcc]), ventral pallidum, and midbrain dopamine neurons. Other structures are core components in regulating the reward circuit, including the dorsal prefrontal cortex (PFC), amygdala, hippocampus, thalamus, lateral habenular nucleus, and specific brainstem structures such as the pedunculopontine and raphe nuclei.[50-53]

Relationship between dysfunction of the reward-processing network and anhedonia in depression

Altered functional connectivity within reward-processing network observed in patients with MDD and anhedonia provides evidence that reward processing is dysfunctional in anhedonia.[49,51,54-62] Functional neuroimaging data primarily underscore the changes in neural activation and functional connectivity during reward processing. Regarding altered activation, anhedonia was found to be significantly negatively correlated with medial OFC activation in adolescents with MDD.[63] Anhedonia in patients with MDD has been associated with decreased activity in limbic regions such as the NAcc and caudate nucleus, and with hyperactivity in cortical regions such as the ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal cortex (dlPFC).[64,65] A review of anhedonic subtypes associated striatal hypoactivation—along with hypoactivation and hyperactivation of several prefrontal regions—with reward-liking and desire, and the blunted sensitivity of the prefrontal striatum to positive feedback with reward learning.[52] Additionally, increased low-frequency fluctuations in the left dorsal anterior cingulate cortex (dACC) were correlated with anticipatory anhedonia in patients with MDD.[66] Regarding changes in functional connectivity, anhedonia was negatively correlated with connectivity to the vmPFC and various reward regions in patients with MDD, including the NAcc, ventral tegmental area, OFC, and insula.[67] Changes in the functional connectivity of frontostriatolimbic circuits and cortical networks may be associated with MDD combined with anhedonia.[68] However, conflicting findings have been reported regarding the relationship between anhedonia and connectivity between the NAcc and the default-mode network (DMN). Reduced reward sensitivity (e.g., reward-liking, motivation, and pleasure) as measured using the Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) scale[69] was associated with a decreased resting-state NAcc connectivity to the DMN and increased connectivity to the salience network across psychiatric conditions, including patients with MDD.[70] Conversely, enhanced functional connectivity between the DMN and NAcc in subthreshold depression was positively correlated with loss of interest, as measured by the two anhedonia items on the Center for Epidemiological Studies-Depression scale.[71] However, it should be remembered that these discrepant findings regarding NAcc−DMN connectivity may be due to differences in anhedonia measures applied in different studies or in the severity of depressive symptoms between the included subjects.

With respect to structural brain changes, several structural magnetic resonance imaging studies have revealed correlations between anhedonia and the reward network. Brain volume reductions in the reward networks (e.g., striatum, NAcc, fornix, and right basal forebrain), decreased white-matter integrity in reward-related brain regions, and reduced cortical thickness (e.g., in the left rostral anterior cingulate cortex and lateral OFC) have been associated with MDD combined with anhedonia.[66,72-79] Additionally, trait anhedonia has been linked to decreased volumes of the caudate nucleus[80] and NAcc[81] in nonclinical cohorts, and the bilateral volume reduction of the putamen has been utilized in predicting anhedonia severity.[81]

BRAIN NETWORK CHANGES AFTER BA AND PREDICTORS OF BA TREATMENT RESPONSES IN fMRI STUDIES ON DEPRESSION

Brain network changes after BA treatments in depression

Previous fMRI studies have examined the neural responses following BA treatments to elucidate their underlying neural mechanisms. Dichter et al.[82] using a probabilistic monetary decision-making task comprising selection, anticipation, and feedback phases, and noted that patients with MDD showed activation changes in the frontal, temporal, and occipital regions associated with reward processing after receiving brief behavioral activation therapy for depression (BATD).[83] The

low activation of the putamen neural circuit observed in anhedonia[58] normalized (i.e., increased) during the reward-selection phase. During the reward-anticipation phase there was increased activation of the left caudate nucleus (i.e., the dorsal striatum), which is strongly associated with reward processing (Table 1).[50] Dichter et al.[84] applied fMRI to the same subjects as in their earlier study[82] and observed that patients with MDD who received BATD showed reduced activation of the prefrontal regions in response to cognitive control stimuli presented in sad contexts (Table 1). The finding of decreased prefrontal activation following psychotherapy contrasts with studies of the effects of psychopharmacological interventions in MDD typically showing increased prefrontal activation.[85-88] These results are consistent with those of previous studies showing decreased prefrontal activity in response to cognitive control stimuli presented in sad contexts to patients with MDD following antidepressant treatment.[89,90] Additionally, the medial prefrontal cortex (mPFC), dlPFC,[91] and occipital cortex[92] have been shown to be hyperactivated in response to negative versus neutral pictures in depression, and overrecruitment of the mPFC during transient sadness may reflect disturbed mood regulation.[93] Thus, the therapeutic effects of BA may be attributable to normalization of the hyperactivity in prefrontal regions within negative or sad contexts.

Other studies have also found changes in regions primarily related to emotion regulation and executive control networks, with these changes differing from those reported by Dichter et al.[84] Mori et al.[94] found that BA treatment increased attenuated neural responses in the left ventrolateral prefrontal cortex (vlPFC) and angular gyrus during loss anticipation in a cohort with subthreshold depression. Earlier research had found that vlPFC activation during distracting sad emotions was lower in patients with MDD than in controls.[95] Additionally, left-lateralized dysfunction is correlated with avoidance and decreased motivation, especially in patients with MDD.[96] BA exerts the strongest and most-varied effects on avoidance modification since it directly addresses the nature of avoidance and specific mechanisms for managing it.[97] Therefore, the increased activations of the left vlPFC and angular gyrus during anticipation of loss after BA treatment may be due to a reduced tendency to avoid loss; that is, an enhanced ability to engage in rewarding behaviors even in aversive situations. In contrast to previous studies,[82,98] Mori et al.[94] found no changes in the reward-related striatum were observed after BA treatment. This discrepancy may be due to differences in depression severity, with participants with subthreshold depression experiencing smaller neural changes than those in the clinical population, and these changes not being reflected in subcortical structures.[94] Similarly, Shiota et al.[99] observed that BA treatment increased activation of the dorsal medial prefrontal cortex (dmPFC) during other-perspective self-referential processing of positive words in participants with subthreshold depression. This increased activation was associated with improved depressive symptoms. Previous research has shown increased mPFC activation in individuals with depression that is associated with increased positive self-reference after CBT,[100] and Shiota et al.[99] replicated these findings using BA treatment. The making of judgements regarding one's future when faced with undesirable information that requires adjusting beliefs about unfavorable future prospects requires the activation of networks that prevent harmful updating, which include the ventral striatum, thalamus, hippocampus, and dmPFC.[101] Thus, dmPFC activation following BA treatment may contribute to preventing unfavorable self-updates and improving objective monitoring, which will alleviate depressive symptoms.

Changes in resting-state functional connectivity (rsFC) have been reported following BA treatments. Yokoyama et al.[102] noted that connectivity of the subnetwork of the anterior DMN that connects to the dACC decreased after BA intervention in participants with subthreshold depression. These decreases were correlated with an increase in the health-related quality of life. The dACC is the core region of the salience circuit[103] that can detect salience changes in internal and external environments, signal the need for further processing, and initiate appropriate cognitive control.[103,104] In contrast, DMN connectivity has been deeply implicated in depressive self-referential processing, such as rumination,[105-109] and hyperfunctioning of DMN circuits has been associated with higher levels of depressive rumination in MDD.[110] BA treatment programs increase access to positive activities accompanied by reinforcement from the environment[111] and provide specific methods to deal with rumination.[30] Therefore, the findings of Yokoyama and colleagues suggest that BA treatments improve the quality of life by activating the dACC, which aids in detecting rewards and choosing positive behaviors, and by controlling the DMN, which is associated with rumination. The BA mechanism may be related to an enhanced ability to use the dACC and DMN independently, which can exert attentional control to favor positive stimuli in the external environment.[102]

Cernasov et al.[112] randomly assigned participants with anhedonic symptoms to BATA[113] and mindfulness-based CT,[114] and estimated changes in anhedonia and rsFC over time using the connectivity between the average regions of interest within the DMN, frontoparietal network (FPN), salience network, and reward network. The results showed significant reductions in anhedonia symptoms and average rsFC within the DMN and FPN over time in the groups receiving

Table 1. Research on changes in brain networks following behavioral activation treatment

Study	Participants	Intervention	Imaging paradigm/ scan time points	Task	BA treatment outcomes
Dichter et al.,[82] 2009	12 Adults with MDD and 15 adults without MDD	8–14 weekly BATD sessions	fMRI/pre- to posttreatment	Wheel of Fortune task: a computerized two-choice decision-making task with probabilistic monetary outcomes, comprising selection, anticipation, and feedback phases	(1) Selection phase - Increased activation of the paracingulate gyrus, left putamen, right supramarginal gyrus, and left posterior temporal fusiform cortex - Decreased activation of the left amygdala, left superior frontal gyrus, left superior occipital cortex, left occipital pole, left postcentral gyrus, left precentral gyrus, left supramarginal gyrus, and right inferior temporal gyrus (2) Anticipation phase - Increased activation of the left caudate, anterior cingulate gyrus, left middle frontal gyrus, left superior frontal gyrus, left lingual gyrus, left lateral and superior-lateral occipital cortex, left posterior parahippocampal gyrus, right insular cortex, right precuneus, right subcallosal cortex, right posterior temporal fusiform cortex, and bilateral precentral gyrus and temporal poles - Decreased activation of the anterior inferior temporal gyrus (3) Feedback phase - Increased activation of the left planum temporale, right superior lateral occipital cortex, and right posterior temporal fusiform cortex - Decreased activation of the left posterior cingulate, left caudate, left postcentral gyrus, and left paracingulate gyrus
Dichter et al.,[84] 2010	12 Adults with MDD and 15 adults without MDD	8–14 weekly BATD sessions	fMRI/pre- to posttreatment	Event-related target-detection task	Decreased activation in response to cognitive control stimuli presented in sad contexts in prefrontal structures, including the paracingulate gyrus, right orbital frontal cortex, right frontal pole, left Heschl's gyrus, left occipital pole, bilateral postcentral gyrus, bilateral precentral gyrus, left superior temporal gyrus, left middle temporal gyrus, right inferior posterior temporal gyrus, and right anterior supramarginal gyrus
Mori et al.,[94] 2016	15 Adults with subthreshold depression and 15 controls	5 weekly BA sessions	fMRI/pre- to posttreatment	Monetary incentive delay task involving gain, loss, and neutral trials	Significant activity increases in the left vlPFC and left angular gyrus for loss anticipation
Shiota et al.,[99] 2017	56 Adults with subthreshold depression randomized to 27 and 29 in intervention and nonintervention groups, respectively	5 weekly BA sessions	fMRI/pre- to posttreatment	Self-referential task: with two viewpoints (self/other) and two emotional valences (positive/negative)	Significant increase in dmPFC activation during other-perspective self-judgement on positive words
Yokoyama et al.,[102] 2018	40 Adults with subthreshold depression randomized to 19 and 21 in intervention and nonintervention groups, respectively	5 weekly BA sessions	rs-fMRI/pre- to posttreatment	Task-free condition: measurements from resting-state echo planar imaging	Reductions in connectivity of the subnetwork of the anterior DMN that connects to the dACC
Cernasov et al.,[112] 2021	73 Participants with anhedonia: 38 and 35 underwent BATA and MBCT, respectively	15 treatment sessions each	7-T MRI/pre- to posttreatment	Task-free condition: measurements of rsFC	Significant reductions in anhedonia symptoms and in the average rsFC within the DMN and FPN over time; however, there is no association between the reduction in rsFC within the DMN and improvements in anhedonia

BA, behavioral activation; BATA, behavioral activation therapy for anhedonia; BATD, brief behavioral activation therapy for depression; dACC, dorsal anterior cingulate cortex; DMN, default-mode network; dmPFC, dorsal medial prefrontal cortex; fMRI, functional magnetic resonance imaging; FPN, frontoparietal network; MBCT, mindfulness-based cognitive therapy; MDD, major depressive disorder; MRI, magnetic resonance imaging; rsFC, resting-state functional connectivity; rs-fMRI, resting-state functional magnetic resonance imaging; vlPFC, ventrolateral prefrontal cortex.

the different interventions. BATA-induced reductions in rsFC within the DMN were consistent with the findings of Yokoyama et al.[102] However, no relationship was observed between within-person reductions in rsFC within the DMN and improvements in anhedonia. Previous studies have produced inconsistent results for the changes in rsFC within the DMN and symptom reduction after depression treatment (e.g., antidepressants and transcranial magnetic stimulation).[115-118] These unexpected results may be due to DMN modulation having an indirect effect on anhedonia and more directly involving changes in related domains such as rumination.[112] In addition, attenuation within the FPN was unexpected considering that hypoconnectivity in the FPN is an MDD hallmark.[119-121] However, reductions in rsFC within the FPN have been reported in patients with MDD who were treated with mindfulness-based interventions[122] and electroconvulsive therapy.[123] Moreover, studies not involving rsFC have produced evidence of PFC hyperactivation during working-memory tasks in MDD.[124,125] Thus, FPN hypoactivation following BA treatment may be related to the alleviation of compensatory forms of dysfunction associated with cognitive overload. An overall schematic of brain network changes after BA treatment in depression can be seen in Fig. 1.

Pretreatment brain network patterns and BA treatment responses

Independent of changes in brain activity patterns following BA treatment, studies have shown that the pretreatment brain activity status is predictive of the treatment effects of BA. Walsh et al.[126] compared the neural connectivity in patients with MDD and healthy controls prior to treatment to investigate the role of global connectivity and connectivity attenuation as predictors of BATD responses. Their results indicated that patients exhibiting more-diverse patterns of brain connectivity (greater global connectivity or connectivity attenuation) in frontostriatal regions relative to controls responded better to BATD (Table 2). Furthermore, the significant clusters were primarily localized in regions within or bordering the dACC and mPFC, which play crucial roles in reward-based decision-making and behavior.[127,128] A subsequent study by Walsh et al.[129] found that reduced connectivity between the left middle frontal gyrus and right temporoparietal regions (which are involved in emotion regulation and selective attention)[130] prior to treatment in MDD patients predicted a greater improvement in anhedonic symptoms following BATD. This is consistent with the earlier work of Walsh et al.[126] suggesting that BATD is more effective in individuals who exhibit greater impairments in reward network function. Overall, patients with deficits in the connectivity of reward-processing-related regions and in the ability to sustain connectivity may especially benefit from the BA treatment model of increasing engagement in goal-directed activities and value-driven behaviors as well as increasing the focus on rewarding activities.[1] Whereas most of these results suggest that individuals with greater disturbances in reward network function benefit more from BATD, normal connectivity patterns predicted better treatment outcomes in the single study of Walsh et al.[126]

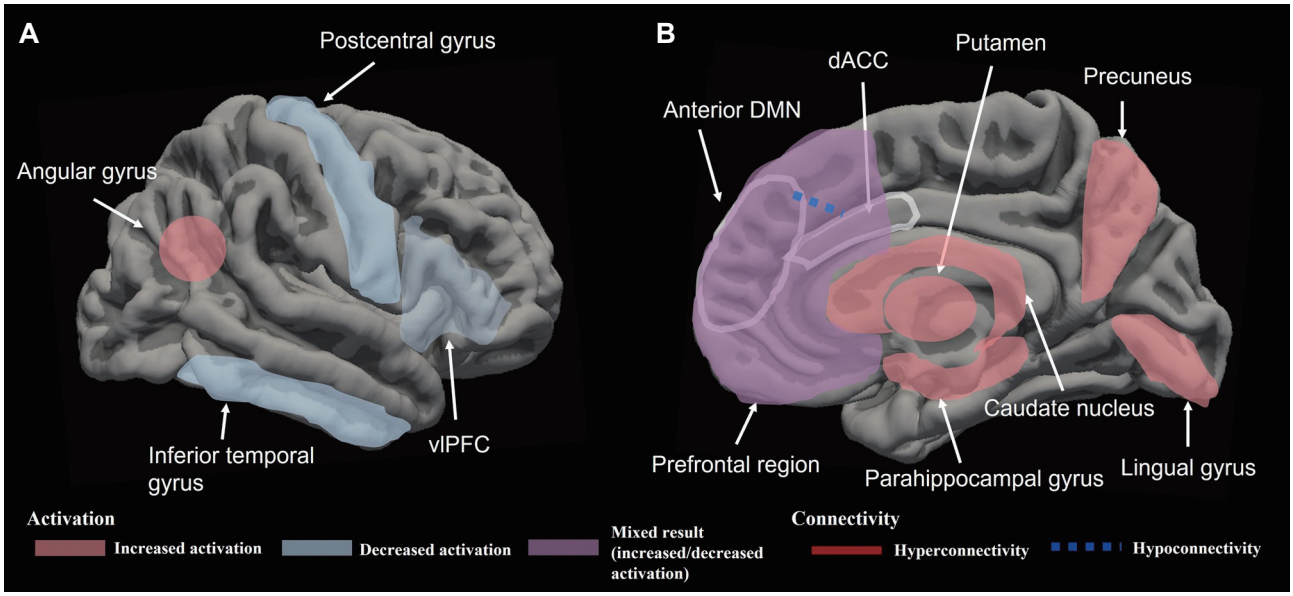

Fig. 1. Schematic representations of the brain network changes following behavioral activation (BA) treatment in lateral (A) and medial (B) views. The brain network changes after BA treatments shown in the figure above are thought to contribute to the reduction in anhedonia and depresive symptoms. dACC, dorsal anterior cingulate cortex; DMN, default-mode network; vlPFC, ventrolateral prefrontal cortex.

Table 2. Research on pretreatment brain network activation patterns as predictors of BA treatment responses

Study	Participants	Intervention	Imagining paradigm/ scan time points	Task	Pretreatment predictor
Walsh et al.,[126] 2017	33 Outpatients with MDD and 20 controls	15 weekly BATD sessions	fMRI/pretreatment	Monetary incentive delay task: anticipation and outcome phases	(1) Diverse patterns in patients compared with controls: - Greater connectivity between the left caudate seed and right paracingulate gyrus during reward anticipation - Greater connectivity attenuation between the right frontal medial cortex seed and paracingulate gyrus during reward anticipation - Greater connectivity attenuation between the left NAcc seed and paracingulate gyrus when receiving a reward outcome (2) Similar patterns in patients compared with controls: - Less connectivity attenuation between the right putamen seed and right OFC/temporal pole during reward anticipation
Walsh et al.,[129] 2019	33 Outpatients with MDD and 20 nondepressed controls	15 weekly BATD sessions	fMRI/pretreatment	Positive-emotions regulation task: passive viewing and positive-upregulation condition	Decreased connectivity between the left middle frontal gyrus and right temporoparietal regions during upregulation of positive emotions
Dichter et al.,[84] 2010	12 Adults with MDD and 15 adults without MDD	8–14 weekly BATD sessions	fMRI/pre- to posttreatment	Event-related target-detection task	Lower activation of the paracingulate gyrus in sad contexts
Webb et al.,[137] 2023	39 Anhedonic adolescents and 41 typically developing adolescents	12 weekly BA sessions	fMRI/pre- to posttreatment	Event-related card-guessing task: win, loss, and neutral trial types	Larger right striatal response to reward

BA, behavioral activation; BATD, behavioral activation therapy for depression; fMRI, functional magnetic resonance imaging; MDD, major depressive disorder; NAcc, nucleus accumbens; OFC, orbital prefrontal cortex.

In contrast to the above studies, other studies have found that intact neuronal responses are predictive of better BA treatment outcomes. The study of Dichter et al.[84] involving patients with MDD found that hypoactivation of the paracingulate gyrus cluster in sad contexts before BATD predicted improvement in depressive symptoms posttreatment. The PFC mediates affect regulation in emotional contexts[131] and several goal-directed behaviors.[132-134] When the task demand increases, PFC activity typically increases in a compensatory manner to ensure that the behavioral performance remains constant.[135] Increased activation of multiple prefrontal regions has been reported in the MDD group in sad contexts,[136] which suggests that a greater cognitive effort is needed from patients with MDD to disengage from sad pictures and respond to a positive stimuli.[125] Thus, hypersensitivity to sad contexts may compromise treatment efficacy by increasing the difficulty in identifying and select rewarding positive activities, because greater cognitive effort is required to respond appropriately to the applied cognitive control stimuli. This suggests that individuals with a lower degree of hypersensitivity would benefit more from BA treatments. Additionally, Webb et al.[137] found that in adolescents with anhedonia, a larger right striatal response pre-BA was associated with a greater improvement in anhedonia posttreatment. In order words, adolescents exhibiting relatively large striatal responses to rewards exhibited better BA treatment outcomes. This is similar to findings obtained when applying CBT for anxiety disorders, where greater striatal responsivity to rewards was associated with symptom improvement.[138] The striatum is involved in reward processing, specifically in learning and updating behaviors that lead to rewards.[139,140] Accordingly, it is believed that individuals with more-responsive reward circuits, such as the striatum, are more likely to engage in reward-focused activities that are addressed in BA (e.g., enjoyable and valuable activities), and that increased reward activity leads to increased pleasure and positive reinforcement, which in turn improves anhedonia.

The association between brain network changes and BA treatment has been primarily investigated using fMRI, with few studies employing other modalities. However, some electroencephalography (EEG) studies have attempted to identify biomarkers for evaluating the effects of BA treatment. Gollan et al.[141] examined alpha EEG asymmetry before and after BA treatment in patients with depression, and investigated how this was associated with emotions. They found that BA treatment did not change frontal alpha EEG asymmetry, which is known to be associated with motivation and emotional affect.[142] However, the pretreatment level of frontal alpha asymmetry was predictive of treatment responses. Specifically, the presence of middle frontal and middle later-

al alpha asymmetry prior to treatment did not predict posttreatment reductions in depressive symptoms, whereas pretreatment middle frontal alpha asymmetry did predict a posttreatment negative mood. These results suggest that BA treatment is less beneficial when greater prefrontal alpha asymmetry is present prior to treatment. Therefore, the pretreatment level of prefrontal alpha asymmetry may serve as a predictor of treatment response and relapse. Additionally, an analysis of resting EEG data by Anderson and Perone[143] identified functional networks associated with the BAS and BIS,[69] which are brain systems that regulate motivation, approach behavior, reward-seeking, and positive affect.[144] That study revealed that the BAS and BIS are associated with different brain networks, with differences in the strengths of these networks potentially accounting for individual differences, particularly in the specific frequency bands (theta and beta) associated with the BAS subscales. Applying this to BA treatment would involve developing a personalized treatment plan by measuring the resting EEG signal to assess the strengths of the networks related to the BAS and BIS. Furthermore, the efficacy of the treatment can be objectively assessed by monitoring the changes in network strength between before and after treatment. In other words, the motivational BAS/BIS has potential as a biomarker for personalized interventions and objective assessments in BA treatment. An overall schematic of the pretreatment brain network patterns indicative of BA treatment response in depression can be seen in Fig. 2.

Limitations of previous fMRI studies on BA and suggestions for future research

There have been few fMRI studies of BA and they have produced inconsistent results. These discrepancies can be attributed to several factors. One possible factor is the different treatment protocols used for BA. For example, Martell et al.[29] emphasized the importance of avoidance in depression and so included techniques to recognize and overcome avoidance in their treatment, whereas BATD[38] does not offer specific techniques for addressing avoidance. Additionally, BATA[44] includes several new components specific to anhedonia, such as removing depression-specific content, adding psychoeducation about anhedonia and responses to rewards, and simplifying activity monitoring for patients with low motivation. Other possible explanations for the differences in study results include sample smallness and different traits being measured in each fMRI study task, such as reward sensitivity, cognitive control, and self-evaluation. Future research should address some of these issues in larger samples and by comparing the findings across multiple fMRI tasks that measure similar properties. Accumulating fMRI data from meta-analytical studies of BA treatment may also lead to the acquisition of consistent findings. For example, a group of researchers specializing in large-scale neuroimaging studies formed the so-called ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) network[145] that has produced reliable and consistent neuroimaging findings by comparing healthy populations with various cohorts having psychiatric disorders including MDD,[146] obsessive-compulsive disorder,[147]

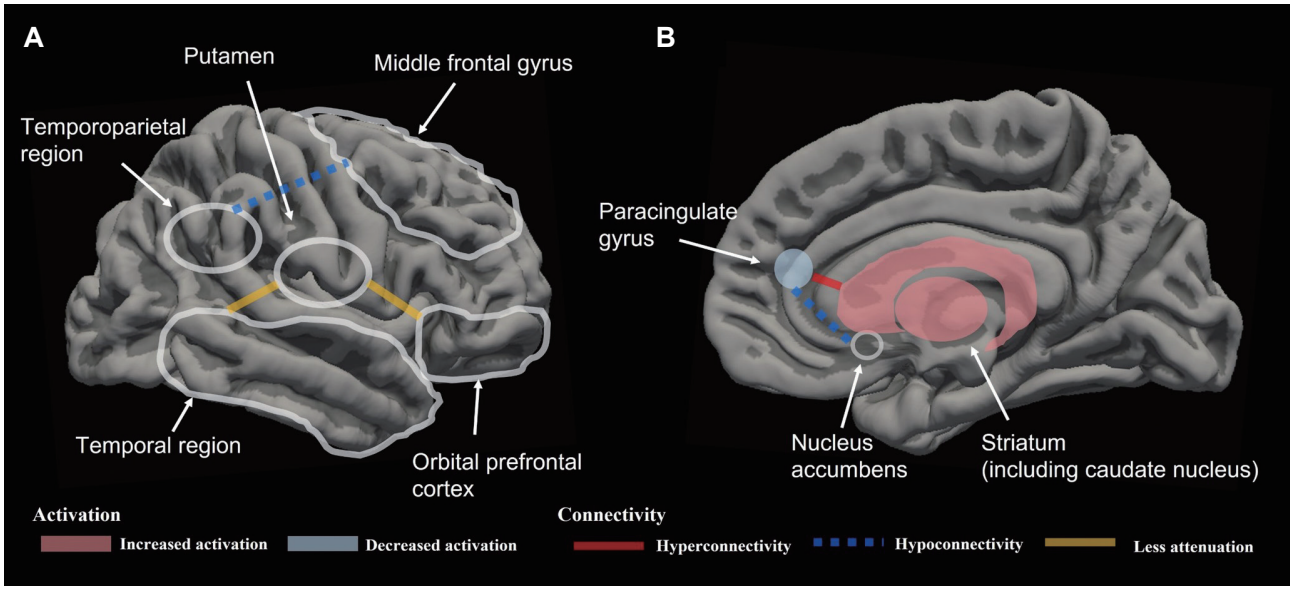

Fig. 2. Schematic representations of the pretreatment brain network patterns that are predictors of larger behavioral activation treatment responses in lateral (A) and medial (B) views. The pretreatment brain activation and connectivity shown in the figure above appears to be assoicated with improved treatment response.

and anxiety disorders.[148] We propose that an fMRI consortium similar to the ENIGMA one could facilitate the identification of reliable neural correlates of BA treatment effects and treatment predictors.

CONCLUSION

The accumulating evidence for the efficacy of BA treatment on depression is leading it to becoming one of the main evidence-based treatments. Technological and conceptual advances in brain imaging have provided new insights into the brain circuits underlying the reward-processing network associated with depression and anhedonia. However, there is a gap between the advances in brain imaging and its application in real-world clinical practice. A literature review addressing neuroimaging endophenotypes can aid in bridging this gap by strengthening the understanding of therapeutic mechanisms for psychiatric disorders and suggesting predictors of treatment responses.

This review has provided insights into the mechanisms underlying BA treatment by revealing how it affects reward-related neural circuits. BA treatment induces increased activation of the prefrontal and subcortical regions (e.g., vlPFC, mPFC, anterior cingulate gyrus, posterior parahippocampal gyrus, insular cortex, and caudate putamen), which are known to be involved in reward processing.[50-53,55,149] The functioning of brain circuits associated with sensitivity to rewards improved posttreatment, reflecting the therapeutic goal of BA of enabling individuals to increase the rewards that they experience in their daily lives.[30] Deficits in regions involved in reward processing are strongly associated with anhedonia and other reward-related deficits.[52,63-67] Together the results suggest that BA treatment induces a series of changes in the brain circuitry that processes rewards so as to increase the responsiveness to positive rewarding behaviors that are meaningful to the individual. Increases in positive rewarding behaviors improve anhedonia, which in turn leads to engagement in behaviors that can lead to greater rewards in life. Furthermore, the prefrontal and subcortical regions that exhibited increased activation after BA have been shown to be involved in reward processing and higher-order cognitive functions, such as problem-solving, decision-making,[150-153] and emotion regulation.[154-157] Thus, the beneficial effects of BA treatment may be due to improvements in reward circuits and the brain circuits that regulate cognitive and emotional responses to problems that are encountered. BA therapy addresses problem-solving, overcoming avoidance, and counteracting rumination that otherwise further entrench depression. These strategies may contribute to improved cognition and emotion regulation, adding to the therapeutic effects of BA.

However, some studies have found decreased activation of the prefrontal regions during cognitive control tasks in sad contexts after BA treatment. This contradictory activation direction may be attributable to studies that show increased activation posttreatment measuring reward selection or expectancy, while studies showing decreased activation posttreatment measure cognitive control in a negative context; that is, these two tasks are measuring different aspects. Prefrontal activation has been associated with exaggerated threat processing in depression and anxiety disorders,[158] and hyperactivation of the mPFC in negative or sad contexts has additionally been reported in depression.[91,93] Therefore, decreased activation of the prefrontal regions posttreatment suggests that BA aids patients with depression to reduce their engagement with negative or sad contexts. Hypersensitivity to sad contexts results in greater cognitive effort being needed to respond appropriately to cognitive control stimuli,[125] which increases the difficulty of identifying and engaging in positive activities. Also, hypoactivation in negative contexts may cause cognitive attention to be diverted elsewhere. Thus, the therapeutic component of BA helps individuals with depression to counteract rumination by refocusing their attention on sensory experiences and positive stimuli.[30]

Studies have also found reductions in rsFC within the DMN after BA treatment. Resting-state analyses of depression have revealed a consistent profile of functional overactivation and hyperconnectivity of the default-mode circuits, with the hyperactivation of default-mode circuits in patients with MDD being strongly associated with maladaptive rumination about depressive thoughts.[110,159] Rumination disconnects an individual from their surrounding real-world environment, causing the individual to become lost in their internal thoughts, ultimately hindering effective problem-solving.[30] Therefore, one therapeutic mechanism of BA involves helping patients to escape from their own internal world, to stop ruminating and to re-engage in activities that are enjoyable and valuable to them.

This review has also provided insights into whether pretreatment reward reactivity or specific neural patterns are predictors of treatment outcomes. Analyses of neurocircuit biotypes can help to differentiate between individuals who respond well to BA treatment and those who do not, and to guide interventions tailored to each individual.[160] Neuroimaging data have been used to perform brain-network-based biotyping to identify patients who may benefit from BA, ultimately enabling precision psychiatry. However, there are two contradictory findings: First, compared with a healthy cohort, improvements in depression or anhedonia were associated with deviations in connectivity between the parac-

ingulate gyrus and left caudate seed, left NAcc seed, and right mPFC seed, and with reduced connectivity between the middle frontal gyrus and right temporoparietal regions, suggesting that BA treatment will be more effective in individuals with functional deficits in their reward network. Second, improvements in depression or anhedonia have been linked to larger right striatal responses, which are associated with reward processing, and lower activation of the paracingulate gyrus, which frees up cognition-regulation resources, indicating that intact neuronal responses to rewards may predict better BA treatment outcomes. These discrepancies can be respectively attributed to the capitalization model, which suggests that individuals with higher pretreatment reward functioning will benefit more from treatment that leverages their existing interest in and motivation to receive rewards, and to the compensatory model, which suggests that individuals with greater deficits in reward functioning will benefit more from treatment.[21] Mixed results supporting the capitalization and compensation models have been obtained for CBT and BA.[161-163] Considering the insufficient and contradictory evidence yielded by previous studies, increasing the benefit of BA treatments will require further research to elucidate the unique characteristics of individuals that determine whether a capitalization or compensation model is appropriate to apply to a specific individual.

Considering neurocircuit biotypes in treatment is consistent with a transdiagnostic and dimensional view of mental disorders, which attempts to understand mental disorders in terms of multiple factors or dimensions rather than categorizing them according to diagnostic criteria. Interventions need to be targeted at the specific neural circuitry of an individual, rather than one-size-fits-all interventions based on the diagnosis only. BA treatment has been found to be effective for depression, anxiety disorders,[164] posttraumatic stress disorder,[165] schizophrenia,[166] substance use disorders,[167] and other conditions, supporting the existence of a transdiagnostic component to the efficacy of this treatment modality. BATA is a transdiagnostic treatment for anhedonia that restores reward motivation and responsiveness in patients with various mental disorders and subthreshold disorders associated with high levels of anhedonia.

Finally, the neuroimaging findings for BA have implications for the development of preventive psychiatry. In a study[168] of adolescents at a high sociodemographic risk of psychopathologies, researchers observed that adolescents with a higher BAS sensitivity[69] exhibited weaker DMN connectivity with the subgenual anterior cingulate cortex (sgACC). Strong DMN–sgACC connectivity is associated with depressive disorders and negative affect,[110,169] suggesting that the sensitivity of the approach-related positive-motivation system is a potential protective factor in the stress vulnerability circuitry of the brain. BA activates and engages individuals in specific ways, allowing them to experience more rewards in their daily lives.[97] BA treatments may therefore aid in preventing the development of stress-related psychopathologies by increasing the BAS sensitivity to achieving goals. Adolescence, in particular, is a developmental period of increased sensitivity in reward-related neural circuits,[170,171] and using an appropriate intervention such as BA during this period may be especially beneficial in preventing future depressive symptoms.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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