*Article*

Behavior Modification
1–28

DOI: 10.1177/0145445518805682
journals.sagepub.com/home/bmo
SAGE

# Reward Network Modulation as a Mechanism of Change in Behavioral Activation

**Gabriela A. Nagy[1], Paul Cernasov[2], Angela Pisoni[3], Erin Walsh[2], Gabriel S. Dichter[2], and Moria J. Smoski[4]**

## Abstract

Behavioral Activation (BA) is a contemporary third-wave psychosocial treatment approach that emphasizes helping individuals become more active in ways that are meaningful to them as a means of improving mood and quality of life. BA has been designated as a well-established, validated treatment for depression by the American Psychological Association following several decades of accumulated empirical support demonstrating that BA techniques successfully reduce depression symptoms and produce other desirable outcomes across a variety of populations and contexts. The purported mechanism of change underlying BA treatment lies in increasing activation, which in turn increases contact with positive reinforcement thereby reversing the cycle of depression. Current studies are further investigating how increasing activation and subsequent contact with mood reinforcers can influence mood and behavior. Specifically, there is growing evidence that BA modifies function of reward-related networks in the brain, and that these changes are associated with clinical improvement. Herein,

[1]Duke University School of Medicine, Durham, NC, USA
[2]The University of North Carolina at Chapel Hill, USA
[3]Duke University, Durham, NC, USA
[4]Duke University Medical Center, Durham, NC, USA

**Corresponding Author:**
Gabriela A. Nagy, Duke University School of Medicine, 2213 Elba St., Box 3026, Durham, NC 27710, USA.
Email: gabriela.nagy@duke.edu

we provide a brief history of BA, describe the primary components of BA treatment, and describe BA's purported mechanisms of change at behavioral, neural, and subjective activation levels. We present limitations as well as gaps in the current state of knowledge regarding mechanisms of action of BA.

**Keywords**
behavioral activation, neural mechanisms, activation, reward processing, anhedonia, major depressive disorder

Behavioral Activation (BA) is a structured and validated contemporary third-wave (i.e., contemporary contextual) psychosocial behavioral treatment approach that emphasizes helping individuals become more active in ways that are meaningful to them, as a means of improving mood and quality of life. Moreover, BA explicitly emphasizes functional behavior analysis and attention to context (Hayes, 2004). BA encourages *activation* by increasing value-guided behaviors and reducing avoidance behaviors to increase contact with potential sources of reinforcement, which often result in significant reductions in clinical symptoms (e.g., depressed mood). Though there is significant empirical support for the clinical efficacy of BA, questions remain about the mechanisms of action of BA, and if knowledge of those mechanisms can be used to further refine and improve treatment success.

## BA's History

BA has its roots in behaviorism (e.g., Ferster, 1973; Lewinsohn, 1974). In the 1970s, various behavioral interventions were developed (e.g., McLean, 1976; Rehm, 1977) in line with behavioral theory (e.g., Lewinsohn, Biglan, & Zeiss, 1976), but this was soon overshadowed by rise of the "cognitive revolution" toward the end of the 1970s, which comprised several studies that evidenced equal or superior effectiveness of cognitive techniques compared with strictly behavioral ones (e.g., Shaw, 1977; Zeiss, Lewinsohn, & Muñoz, 1979). Interest in behavioral treatments for depression symptoms was renewed in the 1990s (e.g., Gortner, Gollan, Dobson, & Jacobson, 1998; Jacobson et al., 1996) and 2000s (e.g., Dimidjian et al., 2006). Findings led to the development of two major variants of BA treatment packages, namely, Martell and colleagues' BA (Martell, Addis, & Jacobson, 2001; Martell, Dimidjian, & Herman-Dunn, 2013) and Lejuez and colleagues' Behavioral Activation Treatment for Depression (BATD; Lejuez, Hopko, Acierno, Daughters, & Pagoto, 2011; Lejuez, Hopko, & Hopko, 2001). For a more

elaborate discussion related to BA's historical background, refer to Dimidjian, Barrera, Martell, Muñoz, and Lewinsohn (2011).

## Empirical Support for BA

Several decades of accumulated empirical support previously led BA to be designated a "well-established, validated treatment for depression" per the by the American Psychological Association (APA) guidelines on determining empirically validated therapies (Chambless et al., 1998). Per an update to these guidelines, BA is now deemed a "treatment pending re-evaluation" (Tolin, McKay, Forman, Klonsky, & Thombs, 2015). Numerous studies have shown that specific BA techniques (e.g., activity scheduling) and the treatment package as a whole are effective for reducing depression symptoms (e.g., Cuijpers, Van Straten, & Warmerdam, 2007; Ekers et al., 2014). For example, a meta-analysis of activation alone (i.e., "activity scheduling") evidenced a large mean effect size (i.e., $d = 0.87$) to control conditions (e.g., cognitive therapy) at posttest and evidenced comparable effect sizes to other psychological treatments and treatment with antidepressants (Cuijpers et al., 2007). Another meta-analysis of individual BA found a large effect across studies ($g = –0.74$), which included randomized controlled trials (RCTs) comparing BA with controls (e.g., waitlist, treatment-as-usual [TAU]) and antidepressant medication (Ekers et al., 2014).

In addition, BA has demonstrated effectiveness in treating depression symptoms in a range of populations, including those struggling with chronic illnesses (e.g., Hopko et al., 2011), other comorbid psychiatric disorders (e.g., Acierno et al., 2016; Jakupcak, Wagner, Paulson, Varra, & McFall, 2010), and co-occurring substance use disorders (e.g., Daughters et al., 2008). Moreover, support has been garnered for the use of BA in a variety of settings beyond individual psychotherapy (e.g., Jakupcak et al., 2010) and with use with a range of modalities beyond face-to-face sessions, such as home-based telehealth (e.g., Acierno et al., 2016). Finally, BA has demonstrated promise as a treatment that could easily be disseminated and implemented with diverse populations within the United States (e.g., Kanter et al., 2015) and globally (e.g., Moradveisi, Huibers, Renner, Arasteh, & Arntz, 2013).

## Activation as the Mechanism of Change in BA

### *Behavioral Indices of Activation*

*Behavioral theory underlying BA.* Consistent with early theoretical writings from Skinner (1953), Ferster (1958, 1973), and Lewinsohn (1974), the behavioral account of depression posits that one factor maintaining it is decreased contact

with stable sources of *positive reinforcement*, or a consequence(s) directly following a behavior that makes that behavior more likely to occur in the future because it is rewarding. Specifically, Lewinsohn (1974) proposed depressed individuals experience reductions or chronically low levels of *response-contingent positive reinforcement*, or positive reinforcement that is dependent on specific behaviors. Loss of contact with positive reinforcement can lead to negative emotional reactions (Kanter, Busch, & Rusch, 2009). In addition, depressogenic behaviors are likely maintained by *negative reinforcement*, or consequence(s) directly following a behavior that makes that behavior more likely to occur in the future by escaping from aversive events (e.g., avoidance). Furthermore, depressed individuals also experience increased levels of *punishment*, or consequence(s) directly following a behavior that that makes that behavior less likely to occur in the future because it is unpleasant. Over time, the depressed individual may be likely to experience low mood, motivation, or pleasure, which may be the result of prolonged aversive reinforcement and punishment schedules (Kanter et al., 2009).

Based on behavioral theory, increasing the frequency of behaviors likely to receive reinforcement should increase response-contingent positive reinforcement, with a subsequent increase in positive affect. As these behaviors are rewarded, their frequency will increase, creating a positive reinforcement cycle. Reward-based learning should improve as patients learn which behaviors are likely to be reinforced. Approach motivation should increase as the potential for reward becomes more likely. As motivation and enjoyment increase, anhedonic symptoms in particular should decrease. Empirical studies provide some support for this model. BA is associated with increased self-reported goal-directed behavior, as measured by the Behavioral Activation for Depression Scale (BADS; Kanter, Mulick, Busch, Berlin, & Martell, 2007) across several trials (e.g., Dimidjian et al., 2017; Hellerstein et al., 2015; Hershenberg, Smith, Goodson, & Thase, 2018; Weinstock, Munroe, & Miller, 2011). Likewise, BA is associated with increased frequency of rewarding experiences, as measured on the Environmental Reward Observation Scale (EROS; Armento & Hopko, 2007) in diverse samples, including substance users (Daughters et al., 2008), veterans (Hershenberg et al., 2018), students (Armento, McNulty, & Hopko, 2012), and pregnant women (Dimidjian et al., 2017). Reductions in measures of anhedonia symptoms have been observed in some (Carl et al., 2016), but not all (Dichter et al., 2009) BA trials. It is important to note that while a purported mechanism of BA is that of *activation*, as outlined above, BA is not exclusively focused on increasing activity levels but also incorporates a variety of other techniques (e.g., problem-solving skills training, mindfulness/"attention to experience" training).

*Empirical support for temporal precedence.* BA has been theorized to lead to clinical improvements as a result of increased activation. However, the evidence for a link between increased BA and decreased depression symptoms has been largely correlational or cross-sectional. Limited evidence for a temporal relationship between activation and depression symptoms comes from a longitudinal observational study of college undergraduates with elevated depressive symptoms (Hill, Buitron, & Pettit, 2017). In that study, availability of potential rewards at baseline predicted depressive symptoms 8 months later, an effect that was mediated by self-reported BA levels 4 months after baseline assessment. A separate study by Santos and colleagues (2017) evaluated activation and depression symptom data from an RCT comparing BA with TAU in a population of Latino immigrants. Using cross-lagged correlation analyses, results showed that the vast majority of clients receiving BA (79%) demonstrated a pattern wherein changes in activation preceded or co-occurred with changes in depression symptoms, yet no clients in the TAU condition evidenced this pattern. Finally, in a study comparing BA with TAU in pregnant women, women who received BA reported significantly higher levels of BA and environmental reward, and early changes in these areas mediated subsequent depression symptom outcomes (Dimidjian et al., 2017).

*Homework completion as a component of activation as a mechanism of change.* Homework completion in BA treatment has been proposed to be a paramount component of BA's purported mechanism of change - activation (Busch, Uebelacker, Kalibatseva, & Miller, 2010). Some have proposed that homework completion may lead individuals to have increased contact with reinforcing events (Addis & Jacobson, 2000), while others hypothesize homework completion may reflect clients' openness to change or enhanced remoralization and hopefulness (Ilardi & Craighead, 1994). Some empirical work has found relationships between homework completion and change in depression symptomatology (e.g., Busch et al., 2010). It is important to note that this finding has not been consistently found. For example, a study of older adults ($N = 20$) employing a brief BA intervention (i.e., 5 weeks) resulted in significant reductions in symptomatology but found no associations among total number of reported activities and their relative proportion of functional, pleasurable, and social activities and improvements in symptoms (Hershenberg, Paulson, Gros, & Acierno, 2015).

## Neural Indices of Activation

*Reward processing systems in the brain.* Anticipation of reward, responsivity to reward once received, and reward-based learning are associated with reward

processing networks in the brain. Reward processing has received significant attention as a pertinent, transdiagnostic dimension of psychopathology. Numerous studies have probed the neural correlates of reward processes in clinical populations, often reporting aberrant activation or connectivity between brain regions in cases relative to controls. However, simple characterizations of hypo- or hyperactive reward processing either within a population (i.e., people with major depression), or even with respect to a symptom (i.e., anhedonia), belie the complexity of this construct.

The neural circuits most closely associated with reward processing are comprised of dopaminergic neurons in the ventral tegmental area (VTA) projecting to the ventral striatum (including the nucleus accumbens [NAc], ventromedial caudate, and ventral putamen), anterior cingulate cortex (ACC), medial prefrontal cortex (MPFC), and orbital frontal cortex (OFC; Berridge & Kringelbach, 2008). The NAc is considered a central hub of this frontostriatal circuit, critical for computing reward value and encoding prediction errors (Gradin et al., 2011). Activation in the NAc is triggered by both primary and conditioned rewards, independent of sensory modality (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000).

Traditionally, a distinction has been drawn between the phases of reward anticipation and reward outcomes. This division receives support from multiple units of analysis, including behavioral self-report and neurophysiological studies (Treadway & Zald, 2011). Neuroimaging investigations of reward processes commonly utilize paradigms capable of examining these phases separately, such as the monetary incentive delay (MID) task (see Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008 for a detailed description), card-value guessing tasks, or other gambling experiments. It should be noted that even reward anticipation may not reflect a unitary construct, but rather multiple perceptual, cognitive, and motor processes coordinated in preparation for potential rewards (Zhang, Li, Wang, Liu, & Zheng, 2017). In addition to differences in anticipation and outcome, reward processing has also been studied in terms of reinforcement learning. Research has compared groups on the relative efficiency of learning cue-outcome contingencies, as well as the response to violations of expected outcomes, otherwise known as prediction errors.

## *Neural Correlates of Reward Processing in Depression and Anhedonia*

Neuroimaging markers of reward processing have been suggested as candidate endophenotypes for depressive syndromes, and specifically for symptoms of anhedonia. One of the most consistent findings reported in the

literature is a blunted striatal response to rewarding outcomes during a depressive episode. This result has been replicated using multiple reward paradigms, various analytic approaches (i.e., whole-brain and region-of-interest functional magnetic resonance imaging [fMRI] analyses), in children (age range = 7-17; Luking et al., 2016; Olino et al., 2014) and in adults. The precise regions of hypoactivation vary from the putamen (Knutson et al., 2008) to the caudate (Forbes et al., 2009; Pizzagalli et al., 2009) to the NAc (Pizzagalli et al., 2009). The fMRI studies have reported decreased striatal response not only comparing averaged signals, but also assessing time-varying activation. Heller and colleagues (2009) demonstrated that individuals with depression were unable to sustain NAc activation while consciously upregulating positive affect. Depressed, but not control, participants showed significant reductions in activation from the first to the second half of emotion regulation trials. Furthermore, these deficits were associated with decreased functional connectivity between the NAc and a region in left middle frontal gyrus during the task. A recent investigation replicated impairments in sustained NAc activation during reward outcomes in adults with depression by comparing earlier and later runs of the MID task within a scanning session (Carl et al., 2016).

With regard to reward outcomes, brain regions beyond the striatum that exhibit functional disturbance in depression include the MPFC, OFC, and insula. The direction of the functional differences reported varies across studies, with some noting hyperactivation of the prefrontal cortex (Forbes et al., 2009; Smoski et al., 2009) and others reporting hypoactivation of prefrontal areas and the insula (Knutson et al., 2008). Prefrontal hyperactivation has been hypothesized to reflect either an attempt at bolstering hyporesponsive striatal structures or an inhibitory signal resulting in overregulation of the striatum. Future studies of functional connectivity are needed to clarify the pattern of prefrontal response to reward outcomes associated with symptoms of depression.

With respect to reward anticipation in major depressive disorder (MDD), some studies report intact striatal responding to reward cues (Knutson et al., 2008; Pizzagalli et al., 2009), while others have shown hypoactivation of the caudate in adults (Smoski et al., 2009) and adolescents with depression (Forbes et al., 2009). The ACC has emerged as another relevant brain region in adults with depression. However, both relative hyperactivation (Knutson et al., 2008) and hypoactivation (Smoski et al., 2009) of this structure has been reported. Patient characteristics may be partially responsible for these discrepant results. Frontrostriatal circuits appear most sensitive to rewards during adolescence, making this developmental period particularly amenable to detecting deficits in reward processing (for a detailed review see Forbes &

Dahl, 2012). Furthermore, the range of anhedonic symptoms likely differed across studies. For example, Knutson and colleagues (2008) did not report measures of anhedonia specifically. It is possible that heterogeneous samples, grouped under the umbrella of depression, may have limited power to detect neural correlates. Another possibility is that the behavioral paradigms themselves account for the varying results. The reward anticipation phase of the MID task entails greater premotor processing than anticipation during gambling paradigms because outcomes are seemingly determined by reaction times in the former versus chance in the latter. Thus, it is noteworthy that studies using the MID task reported no group differences.

Some researchers have looked to reinforcement learning models that consider covariations in neural activity across phases of reward processing. Research has shown an absence of an inverse relation typically observed between ventral striatal activation during reward evaluation and prediction error in adults diagnosed with depression (Greenberg et al., 2015). This covariance has been interpreted as reflecting the shift in neural response as cue-contingencies are learned from primary reinforcers to the predictors signaling potential rewards. Thus, a disruption in this relation may represent a neural basis of deficient learning processes, which have been previously evinced in behavioral studies of depressed individuals (Pizzagalli, Jahn, & O'Shea, 2005). Greenberg and colleagues (2015) also found that greater anhedonia severity was associated with a reduction in this covarying striatal activation. Of note, neither study reported group differences in activation between depressed and control participants during either reward evaluation or prediction error alone, underscoring the importance of assessing *dynamic* functional activity with respect to symptomatology.

While many studies have investigated intrinsic connectivity in depression using fMRI, few have specifically examined the functional connections of the striatum at rest. Attenuated connectivity between seeds in the ventral striatum and the subgenual ACC as well as the ventromedial prefrontal cortex, along with hyperconnectivity between the dorsal caudate and the dorsolateral prefrontal cortex has been observed (Furman, Hamilton, & Gotlib, 2011). A study with depressed adolescents showed relatively increased connectivity between multiple striatal seeds and the dorsolateral prefrontal cortex, as well as between the ventral caudate and the ACC (Gabbay et al., 2013). The authors theorized that hyperconnectivity between the striatum and ACC in adolescence may reflect an early compensatory process that changes to a pattern of hypoconnectivity across development. Anhedonic symptoms showed positive correlations with connectivity strength between the caudate and multiple brain regions, including the pregenual ACC and medial frontal gyrus, however, negative correlations were also reported with connectivity

between the NAc and the subgenual ACC. Interestingly, anhedonia was associated with patterns of functional connectivity distinct from those associated with total depressive symptomatology. Kumar and colleagues (2018) investigated connectivity between the VTA and the striatum during a monetary incentive learning task in unmedicated individuals with MDD. Relative to control participants, individuals with MDD were marked by impaired reward learning (fewer selections of highly rewarded options), reduced VTA-striatum connectivity during reward feedback, and reduced reward prediction error signaling in the striatum.

In a large multisite sample, Drysdale and colleagues (2017) defined four subtypes of depression associated with abnormal resting state connectivity patterns and distinct clinical profiles using canonical correlation analyses. The two subtypes associated with greater anhedonia and psychomotor retardation were marked by hyperconnectivity in thalamic and frontostriatal networks. Moreover, the authors suggested that connectivity features could be leveraged to differentiate treatment responders to repetitive transcranial magnetic stimulation from nonresponders more efficiently than anhedonia or other clinical features.

Caution must be exercised when interpreting the findings from cross-sectional studies of currently depressed versus control participants. These designs obfuscate whether neural signatures reflect stable individual differences in reward processing or episodic changes associated with anhedonic or depressed states. To that end, several studies have reported altered neural reward processing in children and adolescents at an elevated risk for depression, with risk typically defined by a history of depression in one or more first-degree relatives. The fMRI studies have found hypoactivation in the ventral striatum during both reward anticipation (Sharp et al., 2014) and outcomes (Luking, Pagliaccio, Luby, & Barch, 2016). Electroencephalography (EEG) research has also demonstrated a blunted neural response to reward outcomes in youth at risk. Reduced feedback negativity amplitude during positive prediction error has been associated with a maternal history of depression diagnosis in a large sample of 9-year-old children (Kujawa, Proudfit, & Klein, 2014) and has prospectively predicted onset of depressive episodes at 2 years follow-up in a sample of adolescent females (Bress, Foti, Kotov, Klein, & Hajcak, 2013). Thus, neural alterations in reward processing may reflect trait-like vulnerability factors for depression.

Studies of individuals with a history of depression suggest that neural reward processing does not necessarily normalize during remission. Hypoactivation in ventral striatum and ACC in response to the sight and taste of chocolate (McCabe, Cowen, & Harmer, 2009), as well as in the OFC, right frontal pole, and left insular cortex during reward outcomes of the MID task

(Dichter, Damiano, & Allen, 2012) have been associated with remitted depression. Hyperactivation during reward anticipation has also been found in regions including the ACC and right middle frontal gyrus using the MID task (Dichter et al., 2012), and the superior frontal gyrus, hippocampus, and amygdala (Ubl et al., 2015) during gambling tasks. A limitation of these studies is that prior treatments are not specified in detail. Interventions targeting different mechanisms of psychopathology may ameliorate symptoms of depression without affecting other vulnerability factors. Clinical trials targeting motivational and hedonic deficits are necessary to demonstrate whether neural reward processing tracks clinical improvement.

Finally, it is noteworthy that a number of morphometric analyses have found relations between striatal size (adjusted for intracranial volume) and anhedonia severity. Cross-sectional studies show negative correlations between symptoms of anhedonia in depressed adults and caudate (Pizzagalli et al., 2009) and NAc (Wacker, Dillon, & Pizzagalli, 2009) volumes. A recent study in adolescent females replicated the association between NAc volume and anhedonia severity (Auerbach et al., 2017). In this sample, reduced putamen volume was predictive of increases in anhedonic symptoms over a 3-month follow-up. A study of older adults also showed that left putamen volume was significantly reduced in depressed individuals compared with control subjects, and that anhedonia symptoms were inversely related to bilateral putamen size (Sachs-Ericsson et al., 2018). Altogether, these results suggest that reduced striatal volumes may be vulnerability factors specific to symptoms of anhedonia.

*Neural mechanisms of treatment response to BA treatment.* Research into the neural patterns of treatment response in depression are consistent with the notion that depression is a disorder of corticolimbic networks. A recent meta-analysis of task-based and resting state fMRI studies suggests that both psychotherapy and medication result in posttreatment decreases in activation of the right inferior frontal gyrus, superior frontal gyrus, ACC, and right insula (Kalsi et al., 2017). However, unique correlates of treatment response were also identified. Changes in activation in the right paracingulate gyrus differentiated between response to medication versus psychotherapy; decreased activation predicted improved response under medication, while increased activation predicted improved response during psychotherapy (Kalsi et al., 2017). However, studies in this meta-analysis only addressed the effects of interventions on broadly defined depression severity. Few studies have examined the effects of targeted interventions on brain regions relevant to the pathophysiology of core symptoms in depression, such as reward processing deficits or anhedonia.

A growing body of literature has begun to evaluate the brain regions that either predict or are modulated by a response to BA in individuals with depression. While numerous structures are likely implicated in these behavioral modifications, the frontostriatal circuitry underlying approach motivation toward rewarding stimuli is theorized to be of central importance as a mechanism of change. Several neural markers within this circuit have been shown to predict response to BA for depression, including paracingulate gyrus activation during a cognitive control task (Dichter et al., 2009), ACC activation across runs of the MID task (Carl et al., 2016), task-based connectivity between the left putamen and paracingulate gyrus during reward anticipation (Walsh et al., 2017), and resting state functional connectivity between the right insula and right middle temporal gyrus, and between the left intraparietal sulcus and left OFC (Crowther et al., 2015). Interestingly, across the aforementioned studies, with the exception of Walsh et al. (2017), depressed individuals with neural patterns more closely resembling brain function in the control group showed a greater clinical response to BA. For instance, while the depressed cohort evinced a pattern of hyperconnectivity between insular and prefrontal regions, individuals with lower baseline connectivity strength showed a greater reduction in total Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) scores, as well as BDI-anhedonia and BDI-cognitive subscales at posttreatment (Crowther et al., 2015). This was evident despite the fact that clients with more typical brain activation also tended to have more severe pretreatment depressive symptoms. It is possible that alterations in connectivity reflect compensatory mechanisms among individuals with less severe symptoms. This hypothesis is consistent with the finding that individuals with greater depressive symptoms showed greater symptom improvement from BA than individuals with milder symptoms did after controlling for baseline depression (Walsh et al., 2017). To note, studies investigating neuroimaging predictors of response to BA, or change in response to BA, have lacked a comparison condition. Thus, findings cannot be attributed specifically to BA.

Results from investigations into neural outcomes of treatment response to BA align with putative mechanisms of reward processing dysfunction in depression. Dichter and colleagues (2009) evaluated the impact of BATD on distinct phases of reward processing using a Wheel of Fortune Task. Participants with depression completed fMRI scans prepost BATD treatment (average of 11.4/15 weekly sessions) and controls were scanned twice over a similar period of time for comparison. Hamilton Rating Scale for Depression (Hamilton, 1960) scores changed from 23.8 ($SD = 2.3$) to 8.7 ($SD = 9.4$), representing a clinically meaningful response, with 75% of clients classified as treatment responders. Notably, BATD had no impact on behavioral indices

of the reward task (e.g., selection rates between high vs. low probability rewards), affective ratings in response to outcomes, or measures of approach motivation. However, brain imaging revealed that BATD was associated with increased activation during reward anticipation in the left caudate, ACC, as well as numerous frontal, temporal, and occipital cortical regions. Results suggest that BATD may normalize circuits that mediate approach motivation toward reward. Interestingly, neural responses to reward outcomes also showed a Group × Time interaction such that BATD was associated with decreased activation in the left caudate, left posterior cingulate cortex, and left paracingulate gyrus. This result is surprising in the context of extensive literature highlighting a blunted striatal response to reward outcomes in depressed individuals. It may be possible BATD facilitated efficient cue-outcome contingency learning such that clients shifted striatal responding from rewards to cues more quickly than control subjects. However, this interpretation is highly speculative in the absence of correlations between activation during reward anticipation and reward outcomes within relevant striatal structures.

Engagement in goal-oriented behavior requires substantial cognitive control to break habits of avoidance and to approach potentially rewarding contexts. Dichter, Felder, and Smoski (2010) assessed the impact of BATD on neural correlates of cognitive control during a target detection task in the same cohort of participants as their reward processing investigation. Participants viewed a series of sad and neutral images with a rare bull's-eye embedded within the trials requiring a differential motor response. At baseline, depressed individuals showed relatively greater prefrontal activation while responding to targets embedded within the context of sad stimuli than to targets embedded within neutral stimuli, consistent with notions that depressed individuals required greater resources to disengage with the negative affective context. Group × Time interactions revealed a number of prefrontal regions showed decreased activation during the negative stimuli context associated with BATD, including the paracingulate gyrus, right OFC, and right frontal pole. Modulation of the paracingulate gyrus is especially significant given the extensive literature implicating this region as a marker of antidepressant treatment response (Kalsi et al., 2017). Finally, analyses again showed no effects of BATD on behavioral indices of the task such as accuracy, reaction time, or self-reported affective ratings. The absence of BATD impact on behavioral indices, despite changes in depressive symptoms and neural activation, suggests neuroimaging markers may provide more sensitive measures of target engagement for future proof-of-mechanism trials assessing BA interventions for symptom domains such as anhedonia.

## Future Directions

### *BA Across Development*

Adolescence is marked by significantly increased rates of depression onset (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015), and recent work has begun to test the efficacy of BA in adolescent populations (see Martin & Oliver, 2018 for a recent review). To the authors knowledge, however, no studies to date have examined the relationship between reward-related neurocircuitry and BA treatment in adolescents. This will be a critical next step, as reward neurocircuitry is affected by development and may play a significant role in our understanding of how BA may be best applied to adolescent populations.

Neural activation in response to rewards takes an inverted U-shaped curve across development, reaching its peak during adolescence (Somerville & Casey, 2010; Van Leijenhorst et al., 2010). Moreover, recent work has shown that blunted neural responsivity to rewards during adolescence may be a biological marker for risk of depression onset (e.g., Luking et al., 2016; Sharp et al., 2014). Given the heightened sensitivity of reward-related neurocircuitry during this developmental period, it will be important for future research to examine how BA treatment affects reward-related neurocircuitry, and if certain pretreatment neural patterns of reward responsivity predict better or worse outcomes.

It will also be important for future work to examine how different types of activation may have differential impacts on the reward neurocircuitry in adolescents. For example, social stimuli (including social rewards) have been shown to be particularly salient for adolescents (Somerville, Hare, & Casey, 2011). In such circumstances, modified versions of BA focusing specifically on social activation may be a promising next step for the treatment of adolescent depression.

### *Behavioral and Symptom-Specific Measures*

Despite initial evidence supporting the temporal relationship between activation and changes in depression symptom scores, further research is needed to fully elucidate the relationship between changes in BA and changes in symptoms. Specifically, questions remain related to the appropriate time frame required to evaluate the impact of activation and dose of BA treatment needed to make this claim (Santos et al., 2017). Temporal links between activation, reward, and changes in anhedonic symptoms may be further clarified with objective ratings of activation as well as proximal measures (Santos et al.,

2017), such as momentary time sampling and electronic monitoring tools (e.g., Global Positioning System [GPS], pedometer). In addition, behavioral measures of components of reward processing such as effort valuation (e.g., effort expenditure for rewards task [EEfRT]; Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009) and reward-based learning (e.g., probabilistic reward task [PRT]; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008) can provide additional specificity into the aspects of reward that are affected by BA.

Likewise, it will be important for future studies to collect measures related to the subjective experience of reward, specifically those measuring subjective feelings of anhedonia. Although some studies have done this (e.g., Carl et al., 2016; Daughters et al., 2008; Dichter et al., 2009), the majority have measured only depressive symptoms more broadly. One challenge in measuring the anhedonic symptoms theorized to be most affected by BA is the lack of a gold-standard self-report measure of anhedonia. Rather than measuring clinical anhedonia per se, most current measures of anhedonia instead reverse-score measures of hedonic capacity or experiences of pleasures/enjoyment (e.g., the Snaith Hamilton Pleasure Scale [SHAPS], Snaith et al., 1995), which are often content-specific (e.g., Rate how much you would enjoy a cup of tea), were not developed to capture change in clinical populations, and do not tap the full range of loss of anticipation, motivation, and consummatory pleasure that characterizes anhedonia. This limitation reflects the broader challenge that the field lacks a single consensus transdiagnostic definition of clinical anhedonia. Moreover, reverse-score measures (e.g., SHAPS or reverse-scoring the Positive Affect subscale of the Positive and Negative Affect Schedule [PANAS; Watson, Clark, & Tellegen, 1988]) do not distinguish between anticipatory versus consummatory experiences, nor do they capture difficulties in identifying behaviors that have a maximal chance of resulting in reward. Future studies should work to consolidate which assessments of anhedonia may be best suited to measure clinically significant symptoms and symptom changes in transdiagnostic clinical samples.

As it pertains to understanding BA's mechanism(s) of change, it is important to identify mediators and moderators of treatment. These analyses have implications for determining characteristics and processes by which BA can achieve clinical benefit and are consistent with theorized mechanisms (Dimidjian et al., 2017). To that end, Dimidjian and colleagues (2017) recommend future studies incorporate multimethod assessments of putative targets, such as self-report measures of reward (e.g., Carvalho et al., 2011), behavioral tasks (e.g., Treadway et al., 2009), and experience sampling methods. It is advised to test competing models of mediation that investigate processes specified as central to other psychological treatment protocols for depression

to determine BA-specific mechanism(s). Such studies should be powered to test mediation (Dimidjian et al., 2017). In addition, other mechanisms of change outside of increased activation and decreased avoidance should be assessed, including reduced rumination, improved problem-solving, functional-analytic aspects of treatment, acceptance/awareness, and nonspecific therapy factors. Indeed, these aspects of treatment are acknowledged to overlap with the BA approach, though the degree of emphasis on these aspects may differ from other interventions (Martell et al., 2001).

Finally, an additional future direction is to capture in activation measures the idiographic nature of values and their meaning. Stated another way, it is important to develop ways to operationalize and measure increased engagement in meaningful/valued activity when the topography of those activities differs among clients.

## *Neural Indicators*

Neuroimaging measures of reward processes provide a measure of potential neurocognitive mechanisms of BA that have the potential to capture changes not otherwise reflected in self-report or behavioral measures. Though promising, there are some important limitations to using neuroimaging as a mechanistic probe. One challenge is in identifying regions of interest for measurement across time points in a clinical trial. Though the broad frontostriatal reward network has been well-characterized in animal and human studies to date, it is a greater challenge to identify the specific regions that may be affected by BA. In previous studies, there has been some inconsistency between regions that distinguish patients versus controls and regions that change with therapy. As noted in Crowther and colleagues (2015), within regions identified as differentiating patients and controls, greater symptom severity was observed in clinical participants whose activation most closely resembled controls. Thus, greater "normalization" of neural function (i.e., changes in activation or connectivity in clinical participants via BA to more closely resemble nonclinical control participants) may not, in fact, be clinically beneficial. Rather, neural function may change in compensatory ways that instead may deviate further from activation in nonclinical controls. In addition, BA neural targets may not reflect the most etiologically relevant neural processes in all cases of depression symptoms. Depressive disorders are heterogeneous conditions with multiple putative etiologies and manifestations. This point again emphasizes the importance of specifying symptoms thought to be targeted by BA, as neural correlates of symptoms such as anhedonia may have more specificity than depression symptoms more broadly.

Previous neuroimaging studies of BA have been further limited by heterogeneous and small samples, which limit the power to detect treatment effects. Future studies should emphasize patients high in symptoms of anhedonia who are most likely to evince disturbances in neural reward processing targeted by BA. Larger samples should be monitored across multiple time points to capture the temporal relationship between neural and clinical change. Finally, imaging procedures should be optimized to capture frontostriatal regions of interest. The NAc in particular is especially difficult to image effectively due to its small size (1-2 $cm^3$) and proximity to the cerebral sinuses (Neto, Oliveira, Correia, & Ferreira, 2008). Thus, technical improvements in imaging such as the use of 7T fMRI to improve functional signal to noise and blood oxygen level-dependent (BOLD) activation may more closely reflect activity in the capillaries that supply cortical targets of BA.

## *Development of a Novel Transdiagnostic Adaptation of BA Treatment Targeting Anhedonia*

An ongoing clinical trial from our group may serve as an example of how examination of subjective, behavioral, and neurobiological mechanisms can inform treatment development and outcome assessment. Despite BA's efficacy in reducing rates of depressive disorders overall, it is still unclear to what extent BA targets individual depression symptoms. For example, a primary symptom of depression is anhedonia, or deficits in motivation and pleasure. Anhedonia is also implicated in a number of psychiatric illnesses, including mood and anxiety disorders, substance use disorders, schizophrenia, and attention deficit hyperactivity disorder (Dichter et al., 2012). As a result, constructs related to anhedonia are central to the National Institutes of Mental Health (NIMH) Research Domain Criteria (RDoC) project, most notably Positive Valence System constructs of Approach Motivation, Initial Responsiveness to Reward Attainment, and Reward Learning. Anhedonia is often one of the most difficult psychiatric symptoms to treat and thus represents a critical endophenotype and vulnerability factor for a range of psychiatric disorders (Gooding, Tallent, & Matts, 2005; Hasler, Drevets, Manji, & Charney, 2004; Pizzagalli et al., 2005). Given the centrality of anhedonia to a large number of psychiatric disorders, improved interventions to treat motivation and pleasure are a critical public health need. As noted earlier, a central neurobiological substrate of motivation and pleasure is the mesocorticolimbic system (Berridge & Kringelbach, 2008) that is subsumed by projections from the VTA to aspects of the striatum, which drives goal-directed behaviors (Grahn, Parkinson, & Owen, 2008), and to the prefrontal cortex, where the incentive value of stimuli are encoded (Berridge & Kringelbach, 2008). Individuals with anhedonia exhibit impaired responsivity

of the mesocorticolimbic system, yet the translation of these findings to clinical practice has been limited—many pharmacological treatments do not target this system directly and many psychosocial interventions do not focus on improving motivation and pleasure. Moreover, a novel anhedonia treatment is urgently needed given that existing therapies have minimal impact on anhedonia and given the wide range of disorders characterized by anhedonia (Buckner et al., 2008; Dichter et al., 2012).

Thus, our team is currently undertaking steps to adapt the BA framework to treat patients with a range of *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) and subthreshold disorders with high levels of anhedonia, which we call Behavioral Activation Treatment for Anhedonia (BATA). The goal of this trial is to evaluate a transdiagnostic treatment for anhedonia designed to restore reward motivation and responsiveness. Across disorders, anhedonia is associated with impaired mesocorticolimbic activity (Dichter et al., 2012), and this study capitalizes on the innovations of RDoC by recruiting patients with a range of *DSM* and subthreshold disorders with high levels of anhedonia to allow for a transdiagnostic evaluation of this intervention.

In addition to the components of BA treatment outlined previously, the BATA approach incorporates several specific new components. First, content specific to depression is removed and additional psychoeducation about anhedonia and response to rewards is provided. This includes education about anticipatory versus consummatory anhedonia, positive versus negative reinforcement, and how anhedonia can foster avoidance. Second, activity monitoring is streamlined to reduce monitoring effort for low-motivation patients. Third, BATA includes a focus on increased frequency of initiation of new behaviors to target motivation with a module on "dabbling." In line with the objective of increasing behavioral initiation, clients are encouraged to try several new brief activities per week and to take a curious stance toward those activities, monitoring for mild but still present motivation to continue with those behaviors over time, and fostering a sense of acceptance toward their own personal motivational style. The goal of these activities is to accustom the patient to initiating novel activities and to increase sensitivity to more mild forms of approach motivation. Finally, once novel behaviors are established, additional exercises (Hurley & Kwon, 2012; McMakin, Siegle, & Shirk, 2011) are introduced to increase present-moment "savoring" as a means to target pleasure. The spirit of this skill is such that clients are encouraged to deliberately increase focus on the consummatory experience (i.e., intentionally paying attention by noticing information gathered through multiple senses), which is posited to increase contact with possible sources of reinforcement. This concept is similar to the Craske, Meuret, Ritz, Treanor, and Dour (2016) therapeutic approach named Positive Affect Treatment

(PAT), an intervention designed to specifically target deficits in reward sensitivity. These last two elements were specifically chosen to target Positive Valence System constructs of Approach Motivation and Initial Responsiveness to Reward Attainment, respectively.

This intervention is designed to restore reward motivation and reward responsiveness in individuals with clinically impairing anhedonia. Our neurobiological target for this intervention is mesocorticolimbic activation during reward anticipation and reward outcomes measured using BOLD fMRI. Specifically, we hypothesize that, compared with an active control condition of individually administered Mindfulness-Based Cognitive Therapy (MBCT), BATA will be associated with increased striatal activation during reward anticipation and decreased rostral anterior cingulate activation during receipt of reward. These targets are strongly implicated in motivated behaviors and in anhedonia, and we have already shown target engagement in our preliminary data in nonclinical and clinical samples (e.g., Dichter et al., 2009; Smoski et al., 2009). MBCT was chosen as the active comparison condition as it is also a transdiagnostic intervention with demonstrated efficacy in reducing symptoms of depression and anxiety (e.g., Khoury et al., 2013). However, mindfulness-based interventions are thought to operate on fronto-insulo-parietal networks associated with attention and the integration of emotional and physical sensation (e.g., Chen et al., 2015; Goldin, Ziv, Jazaieri, Hahn, & Gross, 2013), rather than by increasing striatal activation.

Thus, to assess the impact of BATA, we evaluate mesocorticolimbic target engagement via functional neuroimaging (utilizing numerous fMRI tasks), subjective ratings of anhedonia (via the SHAPS; Snaith et al., 1995), clinician ratings of symptom improvement (via Clinical Global Impression Severity [CGI-S] and Improvement [CGI-I] scales; Busner & Targum, 2007), functional outcomes (via Short Form-36 Health Survey [SF-36v2]; Ware, Kosinski, Turner-Bowker, & Gandeck, 2007), behavioral measures of reward sensitivity (via the EEfRT; Treadway et al., 2009), and the PRT (Pizzagalli et al., 2008). The trial is currently ongoing, and results have the potential both to inform clinical practice as well as to elaborate means of neurobehavioral modulation of reward network functioning.

## Conclusion

BA is a well-established treatment approach for depression that has high potential to address transdiagnostic symptoms of anhedonia. However, the mechanisms by which BA achieves its effects are not entirely clear. NIMH's RDoC Positive Valence System provides a framework for understanding the behavioral and neural mechanisms by which engagement in valued actions

**Table 1.** Behavioral and Neural Circuitry Units of Analysis in Reward-Based Mechanisms of Change in BA.

| Reward constructs | Relevant neural circuitry | Relevant behavioral tasks | Neurobehavioral effects of BA |
|---|---|---|---|
| Approach motivation/ reward anticipation | Frontolimbic circuit including dorsal and ventral striatum, ACC | EEfRT (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009) | Increased activation in caudate and ACC (Dichter et al., 2009) |
| Responsiveness to initial receipt of reward | Frontolimbic circuit including ventral striatum, ACC, OFC | No established gold-standard task | Decreased activation in rostral ACC (Dichter et al., 2009) |
| Reward learning | Relationship between ventral striatal activation during reward receipt and reward prediction errors | PRT (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008) | Unknown |

*Note.* BA = behavioral activation; ACC = anterior cingulate cortex; EEfRT = effort expenditure for rewards task; OFC = orbital frontal cortex; PRT = probabilistic reward task.

can potentiate reward systems by increasing approach motivation, enhancing initial responses to rewards, and facilitating reward learning. Promising neural targets of BA include mesocorticolimbic reward networks that are associated with different aspects of reward functioning (see Table 1).

As an example of research that can leverage the RDoC framework, we presented an ongoing project evaluating a transdiagnostic treatment for anhedonia designed to restore reward motivation and responsiveness. The BATA modification includes core BA components of facilitating value-guided behaviors and reducing avoidance behaviors to increase contact with potential sources of reinforcement. Additional modules targeting behavioral initiation and savoring of rewarding experiences were added to target Positive Valence System constructs of Approach Motivation and Initial Responsiveness to Reward Attainment. Primary aims of the BATA trial include evaluation of clinical efficacy in reducing anhedonic symptoms as well as impact on mesocorticolimbic reward network activation as a means of better elucidating the treatment mechanisms.

There remain a number of limitations in previous studies as well as gaps in the current state of knowledge regarding mechanisms of action of BA. Though the efficacy of BA as a treatment for depression is well-established, only

recently have clinical trials of BA begun to include measures designed to assess treatment mechanisms. The bulk of studies that do assess mechanistic constructs do so with self-report measures (e.g., Armento & Hopko, 2007; Daughters et al., 2008; Dimidjian et al., 2017; Hellerstein et al., 2015; Hershenberg et al., 2018; Weinstock et al., 2011). Though self-report measures provide critical insight into mechanisms of action, there may be mechanisms of action that cannot be accurately perceived (and thus reported) by patients, including subtle changes in behavior and perception that may be best measured by behavioral and/or biological means. Consistent with the call by Dimidjian and colleagues (2017), we recommend that future studies incorporate multimethod assessments of putative targets such as self-report measures of subconstructs of depression, such as anhedonic symptoms, behavioral tasks, and experience sampling methods. Neuroimaging markers may also be more sensitive to certain aspects of change associated with BA, even in the absence of changes in behavioral indices or self-reported affective ratings, and thus provide an additional important outcome measure for future clinical trials. Our primary recommendation is that, based on the case provided by BA, future proof-of-mechanism trials for established psychotherapies include measures across subjective, behavioral, and neurological units of analysis. BA serves as an example of how constructs based in neuroscience can inform treatment development, as well as how neuroscience can provide important measures of treatment progress and shed light on their mechanisms of effectiveness.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## ORCID iDs

Gabriela A. Nagy https://orcid.org/0000-0001-8176-4341
Paul Cernasov https://orcid.org/0000-0001-7183-393X

## References

Acierno, R., Gros, D. F., Ruggiero, K. J., Hernandez-Tejada, M. A., Knapp, R. G., Lejuez, C. W., . . . Tuerk, P. W. (2016). Behavioral activation and therapeutic exposure for posttraumatic stress disorder: A noninferiority trial of treatment delivered in person versus home-based telehealth. *Depression and Anxiety*, *33*, 415-423.

Addis, M. E., & Jacobson, N. S. (2000). A closer look at the treatment rationale and homework compliance in cognitive-behavioral therapy for depression. *Cognitive Therapy and Research*, *24*, 313-326.

Armento, M. E. A., & Hopko, D. R. (2007). The Environmental Reward Observation Scale (EROS): Development, validity, and reliability. *Behavior Therapy*, *38*, 107-119.

Armento, M. E. A., McNulty, J. K., & Hopko, D. R. (2012). Behavioral activation of religious behaviors (BARB): Randomized trial with depressed college students. *Psychology of Religion and Spirituality*, *4*, 206-222.

Auerbach, R. P., Pisoni, A., Bondy, E., Kumar, P., Stewart, J. G., Yendiki, A., & Pizzagalli, D. A. (2017). Neuroanatomical prediction of anhedonia in adolescents. *Neuropsychopharmacology*, *42*, 2087-2095. doi:10.1038/npp.2017.28

Avenevoli, S., Swendsen, J., He, J., Burstein, M., & Merikangas, K. (2015). Major depression in the national comorbidity survey-adolescent supplement: Prevalence, correlates, and treatment. *Journal of the American Academy of Child & Adolescent Psychiatry*, *54*, 37-44.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-2. *Psychological Corporation*, San Antonio, TX.

Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: Reward in humans and animals. *Psychopharmacology*, *199*, 457-480.

Bress, J. N., Foti, D., Kotov, R., Klein, D. N., & Hajcak, G. (2013). Blunted neural response to rewards prospectively predicts depression in adolescent girls. *Psychophysiology*, *50*(1), 74-81. doi:10.1111/j.1469-8986.2012.01485.x

Buckner, J. D., Joiner, T. E., Pettit, J. W., Lewinsohn, P. M., & Schmidt, N. B. (2008). Implications of the DSM's emphasis on sadness and anhedonia in major depressive disorder. *Psychiatry Research*, *159*(1), 25-30.

Busch, A. M., Uebelacker, L. A., Kalibatseva, Z., & Miller, I. W. (2010). Measuring homework completion in behavioral activation. *Behavior Modification*, *34*, 310-329.

Busner, J., & Targum, S. D. (2007). The clinical global impressions scale: Applying a research tool in clinical practice. *Psychiatry*, *4*(7), 28-37.

Carl, H., Walsh, E., Eisenlohr-Moul, T., Minkel, J., Crowther, A., Moore, T., . . . Smoski, M. J. (2016). Sustained anterior cingulate cortex activation during reward processing predicts response to psychotherapy in major depressive disorder. *Journal of Affective Disorders*, *203*, 204-212.

Carvalho, J. P., Gawrysiak, M. J., Hellmuth, J. C., McNulty, J. K., Magidson, J. F., Lejuez, C. W., & Hopko, D. R. (2011). The Reward Probability Index: Design and validation of a scale measuring access to environmental reward. *Behavior Therapy*, *42*(2), 249-262.

Chambless, D. L., Baker, M. J., Baucom, D. H., Beutler, L. E., Calhoun, K. S., Crits-Christoph, P., . . . Woody, S. R. (1998). Update on empirically validated therapies II. *The Clinical Psychologist*, *51*, 3-16.

Chen, F., Lv, X., Fang, J., Yu, S., Sui, J., Fan, L., . . . Jiang, T. (2015). The effect of body–mind relaxation meditation induction on major depressive disorder: A resting-state fMRI study. *Journal of Affective Disorders*, *183*, 75-82.

Craske, M. G., Meuret, A. E., Ritz, T., Treanor, M., & Dour, H. J. (2016). Treatment for anhedonia: A neuroscience driven approach. *Depression and Anxiety*, *33*, 927-938.

Crowther, A., Smoski, M. J., Minkel, J., Moore, T., Gibbs, D., Petty, C., . . . Dichter, G. S. (2015). Resting-state connectivity predictors of response to psychotherapy in major depressive disorder. *Neuropsychopharmacology*, *40*, 1659-1673. doi:10.1038/npp.2015.12

Cuijpers, P., Van Straten, A., & Warmerdam, L. (2007). Behavioral activation treatments of depression: A meta-analysis. *Clinical Psychology Review*, *27*, 318-326.

Daughters, S. B., Braun, A. R., Sargeant, M. N., Reynolds, E. K., Hopko, D. R., Blanco, C., & Lejuez, C. W. (2008). Effectiveness of a brief behavioral treatment for inner-city illicit drug users with elevated depressive symptoms: The life enhancement treatment for substance use (LETS Act!). *The Journal of Clinical Psychiatry*, *69*, 122-129. doi:10.4088/JCP.v69n0116

Delgado, M. R., Nystrom, L. E., Fissell, C., Noll, D. C., & Fiez, J. A. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology*, *84*, 3072-3077. doi:10.1152/jn.2000.84.6.3072

Dichter, G. S., Damiano, C. A., & Allen, J. A. (2012). Reward circuitry dysfunction in psychiatric and neurodevelopmental disorders and genetic syndromes: Animal models and clinical findings. *Journal of Neurodevelopmental Disorders*, *4*, Article 19.

Dichter, G. S., Felder, J. N., Petty, C., Bizzell, J., Ernst, M., & Smoski, M. J. (2009). The effects of psychotherapy on neural responses to rewards in major depression. *Biological Psychiatry*, *66*, 886-897.

Dichter, G. S., Felder, J. N., & Smoski, M. J. (2010). The effects of brief behavioral activation therapy for depression on cognitive control in affective contexts: An fMRI investigation. *Journal of Affective Disorders*, *126*, 236-244.

Dimidjian, S., Barrera, M., Jr., Martell, C., Muñoz, R. F., & Lewinsohn, P. M. (2011). The origins and current status of behavioral activation treatments for depression. *The Annual Review of Clinical Psychology*, *7*, 1-38. doi:10.1146/annurev-clinpsy-032210-104535

Dimidjian, S., Goodman, S. H., Sherwood, N. E., Simon, G. E., Ludman, E., Gallop, R., . . . Powers, J. D. (2017). A pragmatic randomized clinical trial of behavioral activation for depressed pregnant women. *Journal of Consulting and Clinical Psychology*, *85*(1), 26-36.

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., . . . Jacobson, N. S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *Journal of Consulting and Clinical Psychology*, *74*, 658-670.

Drysdale, A. T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., . . . Liston, C. (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine*, *23*(1), 28-38. doi:10.1038/nm.4246

Ekers, D., Webster, L., van Straten, A., Cuijpers, P., Richards, D., & Gilbody, S. (2014). Behavioural activation for depression: An update of meta-analysis of effectiveness and subgroup analysis. *PLoS ONE*, *9*(6), e100100.

Ferster, C. B. (1958). Reinforcement and punishment in the control of human behavior by social agencies. *Psychiatric Research Reports*, *10*, 101-118.

Ferster, C. B. (1973). A functional analysis of depression. *American Psychologist*, *28*, 857-870.

Forbes, E. E., & Dahl, R. E. (2012). Research review: Altered reward function in adolescent depression: What, when and how? *Journal of Child Psychology and Psychiatry*, *53*(1), 3-15. doi:10.1111/j.1469-7610.2011.02477.x

Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., . . . Dahl, R. E. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *American Journal of Psychiatry*, *166*(1), 64-73. doi:10.1176/appi.ajp.2008.07081336

Furman, D. J., Hamilton, J. P., & Gotlib, I. H. (2011). Frontostriatal functional connectivity in major depressive disorder. *Biology of Mood & Anxiety Disorders*, *1*, Article 11. doi:10.1186/2045-5380-1-11

Gabbay, V., Ely, B. A., Li, Q., Bangaru, S. D., Panzer, A. M., Alonso, C. M., . . . Milham, M. P. (2013). Striatum-based circuitry of adolescent depression and anhedonia. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*, 628-641. doi:10.1016/j.jaac.2013.04.003

Goldin, P., Ziv, M., Jazaieri, H., Hahn, K., & Gross, J. J. (2013). MBSR vs. aerobic exercise in social anxiety: fMRI of emotion regulation of negative self-beliefs. *Social Cognitive and Affective Neuroscience*, *8*, 65-72.

Gooding, D. C., Tallent, K. A., & Matts, C. W. (2005). Clinical status of at-risk individuals 5 years later: Further validation of the psychometric high-risk strategy. *Journal of Abnormal Psychology*, *114*, 170-175.

Gortner, E. T., Gollan, J. K., Dobson, K. S., & Jacobson, N. S. (1998). Cognitive-behavioral treatment for depression: Relapse prevention. *Journal of Consulting and Clinical Psychology*, *66*, 377-384.

Gradin, V. B., Kumar, P., Waiter, G., Ahearn, T., Stickle, C., Milders, M., . . . Steele, J. D. (2011). Expected value and prediction error abnormalities in depression and schizophrenia. *Brain*, *134*, 1751-1764.

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2008). The cognitive functions of the caudate nucleus. *Progress in Neurobiology*, *86*, 141-155.

Greenberg, T., Chase, H. W., Almeida, J. R., Stiffler, R., Zevallos, C. R., Aslam, H. A., . . . Phillips, M. L. (2015). Moderation of the relationship between reward expectancy and prediction error-related ventral striatal reactivity by anhedonia in unmedicated major depressive disorder: Findings from the EMBARC study. *American Journal of Psychiatry*, *172*, 881-891. doi:10.1176/appi.ajp.2015.14050594

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, & Psychiatry*, *23*, 56-62.

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology*, *29*, 1765-1781.

Hayes, S. C. (2004). Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. *Behavior Therapy*, *35*, 639-665. doi:10.1016/S0005-7894(04)80013-3

Heller, A. S., Johnstone, T., Shackman, A. J., Light, S. N., Peterson, M. J., Kolden, G. G., . . . Davidson, R. J. (2009). Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation. *Proceedings of the National Academy of Sciences*, *106*, 22445-22450. doi:10.1073/pnas.0910651106

Hellerstein, D. J., Erickson, G., Stewart, J. W., McGrath, P. J., Hunnicutt-Ferguson, K., Reynolds, S. K., . . . Wang, Y. (2015). Behavioral activation therapy for return to work in medication-responsive chronic depression with persistent psychosocial dysfunction. *Comprehensive Psychiatry*, *57*, 140-147.

Hershenberg, R., Paulson, D., Gros, D. F., & Acierno, R. (2015). Does amount and type of activity matter in behavioral activation? A preliminary investigation of the relationship between pleasant, functional, and social activities and outcome. *Behavioural and Cognitive Psychotherapy*, *43*, 396-411.

Hershenberg, R., Smith, R. V., Goodson, J. T., & Thase, M. E. (2018). Activating veterans toward sources of reward: A pilot report on development, feasibility, and clinical outcomes of a 12-week behavioral activation group treatment. *Cognitive and Behavioral Practice*, *25*, 57-69.

Hill, R. M., Buitron, V., & Pettit, J. W. (2017). Unpacking response contingent positive reinforcement: Reward probability, but not environmental suppressors, prospectively predicts depressive symptoms via behavioral activation. *Journal of Psychopathology and Behavioral Assessment*, *39*, 498-505.

Hopko, D. R., Armento, M. E., Robertson, S., Ryba, M. M., Carvalho, J. P., Colman, L. K., . . . Lejuez, C. W. (2011). Brief behavioral activation and problem-solving therapy for depressed breast cancer patients: Randomized trial. *Journal of Consulting and Clinical Psychology*, *79*, 834-849.

Hurley, D. B., & Kwon, P. (2012). Results of a study to increase savoring the moment: Differential impact on positive and negative outcomes. *Journal of Happiness Studies*, *13*, 579-588.

Ilardi, S. S., & Craighead, W. E. (1994). The role of nonspecific factors in cognitive-behavior therapy for depression. *Clinical Psychology: Science and Practice*, *1*, 138-156.

Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., . . . Prince, S. E. (1996). A component analysis of cognitive-behavioral treatment for depression. *Journal of Consulting and Clinical Psychology*, *64*, 295-304.

Jakupcak, M., Wagner, A., Paulson, A., Varra, A., & McFall, M. (2010). Behavioral activation as a primary care-based treatment for PTSD and depression among returning veterans. *Journal of Traumatic Stress*, *23*, 491-495. doi:10.1002/jts.20543

Kalsi, N., Altavilla, D., Tambelli, R., Aceto, P., Trentini, C., Giorgio, C. D., & Lai, C. (2017). Neural correlates of outcome of the psychotherapy compared to antidepressant therapy in anxiety and depression disorders: A meta-analysis. *Frontiers in Psychology*, *8*, Article 927. doi:10.3389/fpsyg.2017.00927

Kanter, J. W., Busch, A. M., & Rusch, L. C. (2009). *Behavioral activation: Distinctive features*. New York, NY: Routledge.

Kanter, J. W., Mulick, P. S., Busch, A. M., Berlin, K. S., & Martell, C. R. (2007). The Behavioral Activation for Depression Scale (BADS): Psychometric properties and factor structure. *Journal of Psychopathology and Behavioral Assessment*, *29*, Article 191.

Kanter, J. W., Santiago-Rivera, A. L., Santos, M. M., Nagy, G., López, M., Hurtado, G. D., & West, P. (2015). A randomized hybrid efficacy and effectiveness trial of behavioral activation for Latinos with depression. *Behavior Therapy*, *46*, 177-192.

Khoury, B., Lecomte, T., Fortin, G., Masse, M., Therien, P., Bouchard, V., . . . Hofmann, S. G. (2013). Mindfulness-based therapy: A comprehensive meta-analysis. *Clinical Psychology Review*, *33*, 763-771.

Knutson, B., Bhanji, J. P., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2008). Neural responses to monetary incentives in major depression. *Biological Psychiatry*, *63*, 686-692. doi:10.1016/j.biopsych.2007.07.023

Kujawa, A., Proudfit, G. H., & Klein, D. N. (2014). Neural reactivity to rewards and losses in offspring of mothers and fathers with histories of depressive and anxiety disorders. *Journal of Abnormal Psychology*, *123*, 287-297. doi:10.1037/a0036285

Kumar, P., Goer, F., Murray, L., Dillon, D. G., Beltzer, M. L., Cohen, A. L., . . . Pizzagalli, D. A. (2018). Impaired reward prediction error encoding and striatal-midbrain connectivity in depression. *Neuropsychopharmacology*, *43*, 1581-1588.

Lejuez, C. W., Hopko, D. R., Acierno, R., Daughters, S. B., & Pagoto, S. L. (2011). Ten year revision of the brief behavioral activation treatment for depression: Revised treatment manual. *Behavior Modification*, *35*, 111-161. doi:10.1177/0145445510390929

Lejuez, C. W., Hopko, D. R., & Hopko, S. D. (2001). A brief behavioral activation treatment for depression. *Behavior Modification*, *25*, 255-286.

Lewinsohn, P. M. (1974). A behavioral approach to depression. In R. J. Friedman & M. M. Katz (Eds.), *The psychology of depression: Contemporary theory and research* (pp. 157-178). Washington, DC: John Wiley.

Lewinsohn, P. M., Biglan, A., & Zeiss, A. M. (1976). Behavioral treatment for depression. In P. O. Davidson (Ed.), *Behavioral management of anxiety, depression and pain* (pp. 91-146). New York, NY: Brunner/Mazel.

Luking, K. R., Pagliaccio, D., Luby, J. L., & Barch, D. M. (2016). Depression risk predicts blunted neural responses to gains and enhanced responses to losses in healthy children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*, 328-337. doi:10.1016/j.jaac.2016.01.007

Martell, C. R., Addis, M. E., & Jacobson, N. S. (2001). *Depression in context: Strategies for guided action*. New York, NY: W.W. Norton.

Martell, C. R., Dimidjian, S., & Herman-Dunn, R. (2013). *Behavioral activation for depression: A clinician's guide*. New York, NY: Guilford Press.

Martin, F., & Oliver, T. (2018). Behavioral activation for children and adolescents: A systematic review of progress and promise. *European Child & Adolescent Psychiatry*. doi:10.1007/s00787-018-1126-z

McCabe, C., Cowen, P. J., & Harmer, C. J. (2009). Neural representation of reward in recovered depressed patients. *Psychopharmacology*, *205*, 667-677. doi:10.1007/s00213-009-1573-9

McLean, P. D. (1976). Decision-making in the behavioral management of depression. In P. O. Davidson (Ed.), *Behavioral management of anxiety, depression and pain* (pp. 54-90). New York, NY: Brunner/Mazel.

McMakin, D. L., Siegle, G. J., & Shirk, S. R. (2011). Positive Affect Stimulation and Sustainment (PASS) module for depressed mood: A preliminary investigation of treatment-related effects. *Cognitive Therapy and Research*, *35*, 217-226.

Moradveisi, L., Huibers, M. J. H., Renner, F., Arasteh, M., & Arntz, A. (2013). Behavioral activation v. antidepressant medication for treating depression in Iran: Randomised trial. *The British Journal of Psychiatry*, *202*, 204-211. doi:10.1192/bjp.bp.112.113696

Neto, L. L., Oliveira, E., Correia, F., & Ferreira, A. G. (2008). The human nucleus accumbens: Where is it? A stereotactic, anatomical and magnetic resonance imaging study. *Neuromodulation: Technology at the Neural Interface*, *11*, 13-22.

Olino, T. M., McMakin, D. L., Morgan, J. K., Silk, J. S., Birmaher, B., Axelson, D. A., . . . Forbes, E. E. (2014). Reduced reward anticipation in youth at high-risk for unipolar depression: A preliminary study. *Developmental Cognitive Neuroscience*, *8*, 55-64. doi:10.1016/j.dcn.2013.11.005

Pizzagalli, D. A., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R., . . . Fava, M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *American Journal of Psychiatry*, *166*, 702-710. doi:10.1176/appi.ajp.2008.08081201

Pizzagalli, D. A., Iosifescu, D., Hallett, L. A., Ratner, K. G., & Fava, M. (2008). Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *Journal of Psychiatric Research*, *43*, 76-87.

Pizzagalli, D. A., Jahn, A. L., & O'Shea, J. P. (2005). Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biological Psychiatry*, *57*, 319-327.

Rehm, L. P. (1977). A self-control model of depression. *Behavior Therapy*, *8*, 787-804.

Sachs-Ericsson, N. J., Hajcak, G., Sheffler, J. L., Stanley, I. H., Selby, E. A., Potter, G. G., & Steffens, D. C. (2018). Putamen volume differences among older adults: Depression status, melancholia, and age. *Journal of Geriatric Psychiatry and Neurology*, *31*, 39-49. doi:10.1177/0891988717747049

Santos, M. M., Rae, J. R., Nagy, G. A., Manbeck, K. E., Hurtado, G. D., West, P., . . . Kanter, J. W. (2017). A client-level session-by-session evaluation of behavioral activation's mechanism of action. *Journal of Behavior Therapy and Experimental Psychiatry*, *54*, 93-100.

Sharp, C., Kim, S., Herman, L., Pane, H., Reuter, T., & Strathearn, L. (2014). Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *Journal of Abnormal Psychology*, *123*, 298-309. doi:10.1037/a0036191

Shaw, B. F. (1977). Comparison of cognitive therapy and behavior therapy in the treatment of depression. *Journal of Consulting and Clinical Psychology*, *45*, 543-551.

Skinner, B. F. (1953). *Science and human behavior*. Simon & Schuster. New York, NY: The Free Press.

Smoski, M. J., Felder, J., Bizzell, J., Green, S. R., Ernst, M., Lynch, T. R., & Dichter, G. S. (2009). FMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *Journal of Affective Disorders*, *118*, 69-78. doi:10.1016/j.jad.2009.01.034

Snaith, R. P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith–Hamilton Pleasure Scale. *The British Journal of Psychiatry*, *167*, 99-103.

Somerville, L. H., & Casey, B. J. (2010). Developmental neurobiology of cognitive control and motivational systems. *Current Opinions in Neurobiology*, *20*, 236-241.

Somerville, L. H., Hare, T., & Casey, B. J. (2011). Frontostriatal maturation predicts cognitive control failure to appetitive cues in adolescents. *Journal of Cognitive Neuroscience*, *23*, 2123-2134.

Tolin, D. F., McKay, D., Forman, E. M., Klonsky, E. D., & Thombs, B. D. (2015). Empirically supported treatment: Recommendations for a new model. *Clinical Psychology: Science and Practice*, *22*, 317-338.

Treadway, M. T., Buckholtz, J. W., Schwartzman, A. N., Lambert, W. E., & Zald, D. H. (2009). Worth the "EEfRT"? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS ONE*, *4*(8), e6598.

Treadway, M. T., & Zald, D. H. (2011). Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neuroscience & Biobehavioral Reviews*, *35*, 537-555. doi:10.1016/j.neubiorev.2010.06.006

Ubl, B., Kuehner, C., Kirsch, P., Ruttorf, M., Flor, H., & Diener, C. (2015). Neural reward processing in individuals remitted from major depression. *Psychological Medicine*, *45*, 3549-3558. doi:10.1017/s0033291715001452

Van Leijenhorst, L., Zanolie, K., Van Meel, C. S., Westenberg, P. M., Rombouts, S. A., & Crone, E. A. (2010). What motivates the adolescent? Brain regions mediating reward sensitivity across adolescence. *Cerebral Cortex*, *20*, 61-69.

Wacker, J., Dillon, D. G., & Pizzagalli, D. A. (2009). The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: Integration of resting EEG, fMRI, and volumetric techniques. *NeuroImage*, *46*, 327-337. doi:10.1016/j.neuroimage.2009.01.058

Walsh, E., Carl, H., Eisenlohr-Moul, T., Minkel, J., Crowther, A., Moore, T., . . . Dichter, G. S. (2017). Attenuation of frontostriatal connectivity during reward processing predicts response to psychotherapy in major depressive disorder. *Neuropsychopharmacology*, *42*, 831-843. doi:10.1038/npp.2016.179

Ware, J. E., Kosinski, M., Turner-Bowker, D. M., & Gandeck, B. (2007). *QualiMetric user's manual for the SF-12v2TM Health Survey*. Lincoln, NE: QualiMetric Incorporated.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*, 1063-1070.

Weinstock, L. M., Munroe, M. K., & Miller, I. W. (2011). Behavioral Activation for the treatment of atypical depression: A pilot open trial. *Behavior Modification*, *35*, 403-424.

Zeiss, A., Lewinsohn, P., & Muñoz, R. (1979). Nonspecific improvement effects in depression using interpersonal skills training, pleasant activity schedules, or cognitive training. *Journal of Consulting and Clinical Psychology*, *47*, 427-439.

Zhang, Y., Li, Q., Wang, Z., Liu, X., & Zheng, Y. (2017). Temporal dynamics of reward anticipation in the human brain. *Biological Psychology*, *128*, 89-97. doi:10.1016/j.biopsycho.2017.07.011

## Author Biographies

**Gabriela A. Nagy** is a clinical associate in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center. A primary focus of her research is on extending evidence-based treatments, such as Behavioral Activation, to under-resourced settings to vulnerable populations.

**Paul Cernasov** is an advanced graduate student in the Clinical Psychology Graduate Program in the Department of Psychology and Neuroscience at the University of North Carolina at Chapel Hill.His research interests include neuroimaging assessment of treatment response predictors and mechanisms in depression.

**Angela Pisoni** is an advanced graduate student in the Clinical Psychology PhD Program in the Department of Psychology and Neuroscience at Duke University. Her research focuses on how individuals with psychopathology process and interact with rewards in their environment.

**Erin Walsh** is an assistant professor in the Department of Psychiatry at the University of North Carolina at Chapel Hill School of Medicine. Her current program of research investigates neuroinflammatory contributions to anhedonic symptoms in Major Depressive Disorder.

**Gabriel S. Dichter** is an associate professor in the Department of Psychiatry at the University of North Carolina at Chapel Hill School of Medicine and in the Department of Psychology and Neuroscience at the University of North Carolina at Chapel Hill. He is also the director of the Clinical Affective Neuroscience Lab. He has active programs of research in autism spectrum disorders and affective disorders utilizing behavioral, eye tracking, psychophysiological, and neuroimaging methods to investigate neurobiological mechanisms and treatment response in these conditions.

**Moria J. Smoski** is an associate professor in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center and in the Department of Psychology and Neuroscience at Duke University. Her research interests are focused on emotion regulation and reward processes in psychopathology, primarily in Major Depressive Disorder.