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Behavioral Interventions in Health Neuroscience

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Abstract

Many chronic health concerns (obesity, addiction, stress, chronic pain and depression) have garnered recent attention for their increasing frequency, intractability, and serious health consequences. Because they are often difficult to treat and there are not always effective pharmacological treatments for these conditions, many patients are pursuing behavioral interventions for these conditions. Experimental behavioral intervention studies have shown some efficacy for health, but the mechanisms for these treatments are not well understood. Health Neuroscience is a burgeoning field that seeks to link neural function and structure with physical and mental health. Through this lens, initial studies have begun to investigate how behavioral interventions modulate neural function in ways that lead to improvements in health markers and outcomes. Here, we provide a review of these studies in terms of how they modulate key neurobiological systems, and how modulation of these systems relates to physical health and disease outcomes. We conclude with discussion of opportunities for future research in this promising area of study.

Graphical abstract

Many chronic health concerns (obesity, addiction, stress, chronic pain and depression) have garnered recent attention for their increasing frequency, intractability, and serious health consequences. Initial studies have begun to investigate how behavioral interventions, many patients are pursuing for these conditions, modulate neural function in ways that lead to improvements in health markers and outcomes. Here, we provide a review of these studies in terms of how they modulate key neurobiological systems, and how modulation of these systems relates to physical health and disease outcomes, and discuss future opportunities.

Keywords

interventions; neuroscience; health outcomes; neural systems

Behavioral interventions in health neuroscience

The field of health neuroscience aims to link neural systems with health and disease outcomes. There has been significant growth in cross sectional and longitudinal studies

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linking the brain with peripheral physiological processes and biomarkers,[1–5] as well as health and disease outcomes.[6] While this emerging body of work establishes initial relationships between the brain and markers of health, it is correlational. A key strategy for advancing a causal science linking neural processes with health is to manipulate brain activity, and one way to do so is through behavioral interventions. These behavioral interventions may manipulate brain systems in ways that impact health, aiding in our ability to make inferences about how changing brain systems relate to changes in health over time. While the behavioral intervention health neuroscience literature is still in its infancy, this review describes what we know about how behavioral interventions modulate neural systems, and how these changes in neural activity relate to health.

This review is organized by neurobiological systems and focuses on studies that explore how behavioral interventions affect the brain using functional analyses (see Tables 1–4). Thus, we have included studies that used task-based functional analyses, or those analyses that assess brain activity during specific tasks, and resting state connectivity, or those analyses that assess dynamic brain activity while participants are not actively engaged in a specific task. While there are exemplary studies of how acute manipulations of behavior impact the brain[7,8] and how trait-level tendencies affect brain activity,[9,10] this review focuses exclusively on longer-term behavioral interventions (multiple days or weeks) aimed at changing the brain and health outcomes. These behavioral interventions include mindfulness meditation, cognitive behavioral therapy, diet, and exercise interventions, among others. Furthermore, we have prioritized studies in which functional magnetic resonance imaging (fMRI) scans were collected both before and after the intervention to evaluate intervention-related changes within the same participants, but there are also studies comparing brain activity at one time point following an intervention compared to a control.[11–13] While we describe clinical samples (e.g., obese individuals, depressed patients, fibromyalgia patients), we also highlight work using preclinical samples (e.g., healthy young adults, age-matched individuals without disease), which provide a meaningful translational step between cross-sectional or experimental studies and health interventions. After reviewing this emerging behavioral intervention health neuroscience literature, we conclude with some ideas for future research.

Plausible neurobiological systems

Basic research has revealed a few critical neurobiological systems that drive health, and are important candidate neural systems that could be changed with behavioral interventions. These systems are linked to biology, health behaviors or affective states, and could serve as potential mediators for intervention effects on health. These candidate neural systems include the threat and stress system, pain system, reward system, and the self and regulation system (Fig. 1). It is important to note there is some overlap between these systems, and some regions play important roles in multiple systems. Furthermore, the role each region might play in each system may be different, and there may be specificity in spatial location within the region depending on function (e.g. the central nucleus of the amygdala for stress, and the basolateral amygdala for reward).[14]

Threat and stress system

It is well established that the brain coordinates fight-or-flight responses to stress, and this response plays an important role in survival, but can also increase wear-and-tear on physiological systems and increase susceptibility to stress-related health and disease outcomes.[15] Behavioral interventions may modulate the threat and stress system in two ways: by buffering stress reactivity responses (turning down activity in limbic structures that gate the central fight-or-flight stress response), or by increasing top-down regulatory signals (increasing activity in cortical structures that gate top-down control of central fight-or-flight stress response). If behavioral interventions can modulate neural threat system dynamics, it would be expected that mitigating hyperactive or recurrent activation of the threat system could reduce peripheral stress response cascades and their associated effects on increasing risk for stress-related disease.[16,17]

The primary regions involved in stress and threat responding (Fig. 1, panel A) include those regions that detect threat and stress and those that translate this signal into peripheral stress responding via the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis. These regions include the amygdala, dorsal anterior cingulate cortex (dACC) and the anterior insula (AI), along with regions such as the hypothalamus and brainstem, which coordinate physiological stress response cascades.[18] The amygdala is involved in fear and stress, and plays a role in the HPA axis and ANS responses to threats, through projections to the hypothalamus and brainstem.[19] Moreover, one study has found that hyperactivation of the amygdala is associated with posttraumatic stress disorder (PTSD), social phobia and other mental health conditions.[20] One role of the dACC is in conflict detection and affective feelings of distress, including those following from threat or pain,[21] and may affect the SNS arousal and HPA axis activity via projections to the amygdala and brainstem.[22] The subgenual anterior cingulate cortex (sgACC) has also been implicated in emotional processing, and is linked to mood disorders.[23,24] The sgACC has connections with the amygdala and other limbic structures, and research has shown that the stronger these functional connections, the more physiological stress reactivity to stressors.[25,26] Finally, the hypothalamus and brainstem serve as critical hubs linking higher-level cortical representations of stress with the generation of peripheral physiological stress response cascades in the HPA axis[272625272416] and ANS.[27,28] There are some promising initial studies, described below, which suggest that behavioral interventions can reduce reactivity and connectivity in regions in the threat system.

Pain system

Similar to threat and stress, pain is an important survival signal. Indeed, pain is thought to be a signal to avoid or remove the painful stimulus.[29] Experiencing pain thus activates physiological systems to help mobilize the individual to avoid the painful stimulus, but chronic neural activation can lead to burdensome hyperactivation of these physiological systems. Chronic pain conditions are thus marked by negative affect and downstream health consequences, and behavioral interventions have been shown to be helpful in reducing these consequences.[30,31] Pain is often divided into four components: nociceptive/sensory signals that indicate the source and location of pain, perception (how the individual subjectively experiences the pain), the emotional experience (suffering), and the subsequent behaviors

(i.e., removing or avoiding the pain stimulus).[30] Behavioral interventions are most likely to affect pain perception and emotions primarily, which could lead to changes in behavioral and physiological responses to pain.

Experimental and clinical brain mapping work has demonstrated that the sensory, affective and subsequent emotions of pain interact and rely on overlapping neural regions (Fig. 1, Panel B). Specifically, nociceptive responses to pain are meditated by regions such as the somatosensory area, insula and the posterior parietal cortex, followed by arousal and autonomic activation via amygdala, hypothalamus and the supplementary motor area (SMA).[32] The AI is believed to be involved in interoceptive processes that lead to pain awareness.[33,34] Specifically, the AI can serve to detect physiological arousal, linking pain signals to pain responding in the brain, via projections to the amygdala.[35] The affective experience of pain seems to be associated with increases in the dACC and AI activity and subsequent emotions rely on prefrontal cortex (PFC) regions including the medial PFC (MPFC).[21]

Reward system

Adaptive behaviors, such as eating, reproduction and social connection, are key to survival and these important behaviors are reinforced via dopaminergic and opioidergic pathways in the central nervous system, dubbed the reward system.[36] While reinforcement of these survival behaviors is adaptive when helping achieve homeostasis, sometimes these behaviors are reinforced past the point of homeostasis leading to obesity, addiction and other health conditions.[37] Behavioral interventions could reduce the reinforcement of unhealthy behaviors, or help maximize the reinforcement of healthy behaviors via the brain's reward system.

The reward system is a well-characterized and conserved mesolimbic dopamine pathway,[38] and human neuroimaging research has identified a few key hubs (Fig. 1, Panel C). The ventromedial PFC (VMPFC) is involved in processing valuation of a stimulus,[38] and is known to inhibit threat and fear responding, including in fear extinction and pain.[39–41] The orbitofrontal cortex (OFC) is also involved in reward-related processing.[42] (The VMPFC and OFC are sometimes labeled interchangeably in human neuroimaging studies.) The ventral striatum (VS) is a collection of regions within the basal ganglia mesolimbic system including the caudate nucleus, the caudate head, the nucleus accumbens (NAcc), and ventral portions of the putamen.[43] The VS has connections to the thalamus and hypothalamus suggesting a plausible pathway from this region to downstream physiology.[44] Other regions, including the insula and amygdala, have also been implicated in reward processing.[45–47]

The regions involved in the reward system can play an important role in biological systems underlying health, and moreover, reinforce behavior. The reward system serves to reinforce important survival-related behaviors, but dysregulation in this system is linked to a variety of poor health outcomes including obesity, PTSD and addiction[48].

Self and regulation system

The "self" has been studied extensively in psychology and refers to a collection of processes that aid in how an individual understands himself/herself and engages with the world around

them, including behaviors and processes such as self-awareness, self-knowledge, and self-control [49]. Typically, individuals are motivated to behave in ways that are consistent with their self-concept,[50] and thus self-related processes are often associated with self- and emotion regulation, necessary strategies for regulating behavior. Indeed, the individual's self-concept and regulation behaviors are critically important for mental health outcomes and important health behaviors. For example, higher self-control is predictive of healthier eating behaviors and better weight loss,[51] and more positive self-perceptions about aging lead to more preventative health behaviors and improved functional health in older adults.[52,53] A collection of regions in the brain (described below) have been identified as key regions involved in self and regulatory processes, and here we refer to this system of regions as the self and regulation system. Behavioral interventions can modulate the self and regulation system in important ways for subsequent behavior and health. Interventions could increase activity in this system, which could lead to better self- and emotion regulation, or reduce activity in this system to negative self-concepts. Either of these patterns of modulation within the self and regulation system plausibly leads to adjustments in behaviors and health outcomes.

The medial PFC (MPFC) is the primary neural region associated with thinking about oneself, and self-knowledge,[54] and this region is linked to subsequent behavior, including health behaviors.[55] Research also implicates the dACC in detecting conflicting information or representations of the self.[56] Self-control is an important aspect of reducing (or never beginning) unhealthy behaviors, and the dorsolateral PFC (DLPFC), has been linked to self-control and decision making.[56,57] Regions involved in self-regulation include the dorsomedial PFC (DMPFC), posterior cingulate cortex (PCC), and the VMPFC (Fig. 1, Panel D).[58–60] Beyond self-regulation behaviors, negative affect can also have both biological and behavioral effects on health, including increases in the sympathetic nervous system (SNS) activity and impaired decision-making abilities,[61,62] emphasizing the importance of effective emotion regulation arising from the self. The ventrolateral PFC (VLPFC) has been shown to be one of the central regions involved in emotion regulation, particularly the right VLPFC.[63] Additional emotion regulation regions include DMPFC, DLPFC and dACC.[63]

Some of the most significant advances in behavioral intervention health neuroscience research consist of links between activation of the self and regulation system and health behavior outcomes (e.g., smoking).[64] Importantly, as we review below behavioral interventions that affect the self and regulation system (also see Table 4), intervention research in this area has shown that activity in the neural self and regulation system is predictive of health behaviors, and that reducing activity to negative self-beliefs may have important mental health benefits.

Studies linking behavioral interventions, the brain, and health

While the study of behavioral interventions is a relatively new area of health neuroscience, there are a collection of studies linking intervention effects to proximal health markers and more distal health and disease outcomes. Here we will review this work, organized by neurobiological system.

Behavioral interventions and the threat/stress neural system

Stress is well established to have important links to poor health.[17] From the perspective of neural systems, if a behavioral intervention could effectively reduce the reactivity of this system, weaken connectivity between regions in this system, or trigger down regulation of this system, it could mitigate activation of the sympathetic–adrenal–medullary (SAM) and HPA axis response cascades and the cumulative wear-and-tear they have on physiological systems and health.[15] Studies of interventions have begun to examine these possibilities using neuroimaging (Table 1).

One way to explore the possibility that behavioral interventions could lead to reduced threat reactivity is to study the effect of an intervention in a highly stressed population: patients with PTSD. Typically the amygdala is involved in threat processing and the VMPFC is involved in facilitating fear extinction.[40] Patients with PTSD show enhanced amygdala activity and reduced PFC activity,[65] this exaggerated reactivity and diminished top-down control suggests dysregulation in the threat system. However, when PTSD patients received cognitive behavioral therapy (CBT), a 12-week intervention aimed at restructuring unhelpful cognitive patterns and building coping skills, this dysregulation was altered. Specifically, PTSD patients after CBT treatment showed an increase in sgACC activity to a threat reactivity task (viewing threatening faces), an association between increased sgACC activity and decreased symptoms, and an association between decreased amygdala activity and decreased symptoms.[66] While these results suggest that a behavioral intervention can alter threat system activity to stress and lead to changes in relevant symptoms, it is not yet clear whether and how this pattern of neural activity directly leads to changes in symptoms.

If amygdala and sgACC activity are important predictors of stress outcomes, it is possible that connectivity between these regions is important as well. Indeed, higher perceived stress is associated with greater amygdala–sgACC resting state functional connectivity.[67] This altered connectivity may also be an important target for behavioral interventions for threat and stress. Mindfulness meditation interventions—which foster awareness and acceptance of present moment experience—have been shown to reduce stress reactivity in behavioral studies[68–70] and thus may be one intervention that could alter neural threat system dynamics. Indeed, after a 3-day retreat-style mindfulness program (compared to a 3-day relaxation control program), stressed adults showed a decrease in the amygdala–sgACC connectivity at rest.[67] Additionally, there was some initial indication that intervention changes in the amygdala–sgACC connectivity were associated with decreases in cumulative (hair-sampled) HPA axis activation, suggesting that altering the neural threat system may play a role in reducing peripheral stress response system dynamics over time.[67]

It is also possible that behavioral interventions can increase top-down regulation of the targeted neurobiological system.[71] For example, there is some initial evidence that mindfulness interventions can increase resting state functional connectivity of regions known to be important in executive control and top-down regulation.[72,73] We recently showed that mindfulness training increases functional connectivity at rest (i.e., the PCC in the Default Mode Network) with regulatory regions of the PFC (DLPFC), relative to a relaxation training comparison group.[72] The DLPFC is a region implicated in emotion regulation,[63] and as such this connectivity pattern may represent a potential strengthening of

top-down executive control after mindfulness training. Notably, we found that this increased connectivity pattern was associated with intervention-driven reductions in inflammation at follow-up.[72] Likewise, in a separate mindfulness intervention study with veterans with PTSD, increased connectivity between the PCC and DLPFC was also associated with reductions in PTSD symptoms,[74] suggesting that these connectivity changes have important implications for both stress biology (interleukin [IL]-6) and stress-related (PTSD) symptoms.

While there is a large cross-sectional literature relating activation of the neurobiological threat system with increased stress and health risks,[15,17] less is known about how behavioral interventions (or stress reduction interventions specifically) might modulate this system. We have described some initial intervention evidence suggesting that this is a promising area of inquiry, particularly since there is a large behavioral literature linking interventions with salutary stress-related health and disease outcomes.[68,75,76]

Behavioral interventions and the neural pain system

Pain is a common and distressing health concern that leads to significant healthcare costs, missed workdays, and decreased quality of life.[77] Moreover, pain that causes patients to have difficulty completing typical daily activities is associated with poor health behaviors—including physical inactivity, sleep insufficiency, and smoking—and greater mental health symptoms.[78] Thus, altering patients' experiences of pain could boost health by helping improve quality of life and facilitating healthy behaviors. With the risks of uncomfortable side effects and addiction with opioid pain relievers and other pharmacological treatments, behavioral interventions might be an important alternative (Table 2). These interventions could lead to changes in neural responses to pain perceptions and pain affect, or could trigger increased neural coping and control mechanisms to manage pain.

In order to explore whether a behavioral intervention could alter perceptions of pain and subsequent affect, some work has used experimentally manipulated pain relevant to a patient's diagnosis. Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder with abdominal pain as one of the hallmark symptoms. Some over-the-counter pain medications can cause irritation in the gut; therefore, many patients seek out alternative therapies for their pain. Gut-directed hypnotherapy has been shown to have some efficacy in alleviating IBS symptoms for patients.[79] To explore the neural mechanism, IBS participants did either a gut-direct hypnotherapy intervention or educational intervention, and completed baseline and post-therapy scans while experiencing high- and low-intensity rectal distensions. Regardless of condition, IBS patients felt similar symptom reduction after treatment.[80] Patients who responded to hypnotherapy treatment showed reduced AI activity to the high intensity distention after treatment compared to baseline, and more of a decrease in AI activity to the low-intensity distention compared to the education group.[80] While this suggests that both hypnotherapy and patient education can reduce symptom burden for IBS patients, hypnotherapy may alter neural pain responding differently than patient education interventions, particularly for experiences of low-intensity pain.

Relatedly, interventions that affect connectivity within this system could also lead to changes in pain symptoms. Fibromyalgia—a condition characterized by chronic, widespread pain—

has increasingly become a condition of interest for intervention studies, as it is difficult to treat. Recent work has found that physical exercise interventions may be effective in reducing pain and fatigue in patients, but the neural mechanisms are poorly understood.[81] Fibromyalgia patients and healthy controls engaged in a 15-week exercise intervention, and completed a resting state scan before and after the intervention. At baseline, the patients showed decreased connectivity between pain and sensorimotor brain regions compared to healthy controls.[82] However, after the intervention, patients showed greater connectivity between the AI and primary sensorimotor areas, and this connectivity looked more similar to healthy controls.[83] This suggests that an exercise intervention can lead to stronger connectivity between pain and sensorimotor regions; however, these changes in neural connectivity were not associated with changes in symptoms. While it is currently unclear how changes in resting state connectivity in the pain system might be linked to changes in chronic pain symptoms, one possibility is that this increase in neural connectivity between a nociception region and a feedback loop may provide for more efficient regulation to decrease pain.

Finally, behavioral interventions for pain could also increase activity in regions associated with cognitive control that could facilitate down regulation of pain responding. One intervention of interest is mindfulness meditation, as there is evidence that mindfulness training can lead to pain relief.[84] In healthy adults, reductions in self-reported pain intensity ratings to a thermal pain probe after a 4-day mindfulness training intervention were associated with increased activity in the ACC and AI; similarly, reductions in self-reported pain unpleasantness after the intervention were associated with increased OFC activity.[85] These findings were replicated again following another 4-day mindfulness training intervention and these effects were observed above and beyond placebo or sham mindfulness meditation comparison groups.[86] Across these two studies, mindfulness meditation pain relief was associated with changes in activity in cognitive control regions, suggesting that mindfulness may also promote activity in top-down regulatory systems to help individuals cope with pain.

Based on these findings, it is possible that behavioral interventions for pain could be relying on neural mechanisms to modify pain responding or to enhance coping to the pain experience. Across two studies with chronic pain patients, interventions were shown to reduce neural pain processing or enhance connectivity within the pain system. Preclinical work found that behavioral interventions could also enhance neural coping resources, although the correlation with pain in daily life for chronic pain sufferers is not yet known. As these two interventions elicited slightly different changes in the pain system (decreasing responding or increasing coping), it is possible that there are multiple mechanisms by which behavioral interventions could affect pain. Moreover, it is possible that certain types of pain or certain patient characteristics could influence which neural mechanisms could lead to beneficial health effects. Understanding the mechanisms for each intervention could provide greater insight into which interventions might be most effective under certain circumstances.

Behavioral interventions and the neural reward system

A broad range of health conditions, including obesity, and substance abuse and addiction, have been linked to reward system dysfunction.[87] Some behavioral interventions have been shown to be modestly effective at treating these disorders and unhealthy behavior patterns.[88,89] If interventions could reduce neural reward responding to poor health behaviors, or enhance reward responding to healthier behaviors, this could lead to improvements in these health conditions (Table 3).

Studies have explored the possibility that behavioral interventions might affect the neural reward reinforcement of unhealthy behaviors. For example, an individual's reward system is implicated in both obesity and resistance to weight loss, as there appears to be relative hyperactivation in the reward system to anticipating high-calorie foods for obese individuals compared to lean individuals.[90] High-calorie foods are known to be more rewarding than low-calorie foods,[91] but individuals who show increased reward activation to viewing these foods are more likely to gain weight.[92] However, recent work from two intervention studies demonstrates that, after a weight loss intervention, obese individuals showed a significant decrease in VS activity to high-calorie versus low-calorie food images at follow-up,[93] and a decrease in activation to high-calorie food images in the MPFC from baseline to follow-up.[94] Moreover, participants who had relatively low insula activity to high-calorie food images at post-intervention, compared to baseline, tended to be more successful at weight maintenance.[94] Similar to weight-loss interventions, acute exercise (compared to no exercise) has been shown to lead to reduced activity to food cues (vs. control) in the OFC, insula and VS,[95] suggesting that an exercise intervention could effectively reduce neural reward responding to unhealthy food. Furthermore, following a walking-based exercise intervention, individuals showed reduced activity in the insula when viewing food cues compared to baseline, and this decrease in insula activity was correlated with greater decreases in body weight and fat mass.[96] In concert, these findings demonstrate that restructuring reward-related neural responding to food cues might be one plausible neural mechanism by which behavioral interventions could lead to changes in obesity-related health outcomes.

Taken together, it seems that, for a health condition (obesity) characterized by exceptionally difficult to change behaviors, interventions that reduced neural reward activity to these unhealthy behaviors may help to lessen the reinforcing nature of them in ways that enhance health. It will be important to investigate whether other behavioral interventions can reduce reward system activity to unhealthy behaviors and lead to improvements in other health conditions. Some behavioral interventions have also been shown to lead to greater engagement in healthy behaviors, such as eating more vegetables.[97] Cross-sectional work has found that reward-related activity is associated with increases in physical activity, suggesting that interventions could also affect health by increasing the reinforcement value of healthy behaviors that may be difficult to maintain over time.[98] Future work in this area could explore whether enhanced reward-related neural activity to engaging in healthier behaviors like this may be a mediator for downstream health benefits.

Behavioral interventions and the self and regulation system

Critical to our health is the ability to understand whether information is relevant to us, as well as the ability to regulate the thoughts, feelings and behaviors that arise during daily life. The role of the self and regulation system in these behaviors is central, and changes in patterns of neural activity in this system may lead to increases in subsequent healthy choices. Behavioral interventions could affect the self and regulation system in important ways for health by increasing activity or connectivity in the system, supporting greater self- and emotion regulation. It is also possible that behavioral interventions could reduce activity in this system to change problematic self-perceptions and reduce negative self-concepts (Table 4).

From public health messaging campaigns to receiving medical advice from a physician, humans are regularly provided important and potentially life-saving health information. In order for the person to engage in the healthy behaviors promoted in these messages, they must see the message as being self-relevant. Recent research has found the more self-related MPFC activity to these health messages, the more people are likely to change their behavior. Specifically this has been demonstrated in health messages to encourage sunscreen use,[55] reduce smoking,[64,99,100] and increase physical activity.[98] The MPFC activity was also shown to be effective in predicting behavior above and beyond self-reports.[64] Importantly, when these health messages are tailored to the individual they are more effective than when they are more generic,[100] supporting the idea that this self-relevance is important for the subsequent behavior change. It may also be the case that other varieties of health messaging (e.g., patient-provider communication or patient health education materials) have similar neural mechanisms, and further research can help explore these possibilities.

One form of self-regulation is emotion regulation, an important strategy that has implications for mental health and behavior.[101] It is possible that behavioral interventions can lead to increases in emotion-regulation activity to negative events; for example, increasing emotion regulation to experiences of pain in fibromyalgia patients. One such study examined the effect of CBT on emotion regulation activity in fibromyalgia patients. Patients were randomly assigned to either CBT or waitlist control; before and after treatment, they completed fMRI scans while receiving pressure pain stimulation. After CBT, fibromyalgia patients showed increased VLPFC activity to pressure pain compared to baseline, but the control group did not see this increase.[102] CBT also led to increased VLPFC–thalamus connectivity, but there was no change in the control group.[102] If the thalamus serves as a major relay hub in the brain, and the VLPFC is an emotion regulation region, increased connectivity between these regions could lead to changes in how pain affects downstream consequences for patients. Indeed, there was a correlation between increased VLPFC activity to pain and decreases in anxiety after CBT treatment.[102] These findings suggest that behavioral interventions could modulate the self and regulation system activity in emotion regulation regions, enhance regulation region connectivity with an important physiological communication hub, and this modulation in activity could be associated with improvements in associated symptoms.

Some health conditions, including major depressive disorder (MDD) have been linked to a bias towards negative social information and pervasive, negative self-thoughts.[103] Thus,

reducing activity in the self and regulation system to these negative stimuli might have implications for mental health outcomes by reducing the likelihood that they continue the cycle of negative thoughts characterized by this disorder. For example, patients with MDD often have shown greater activity in the MPFC during self-referential processing of negative words, whereas healthy controls showed greater MPFC activity to positive self-referential processing.[104] CBT, a well-established treatment for MDD, may help MDD patients restructure negative thoughts about themselves. Following a 12-week CBT program, the activity in MPFC and ventral ACC increased for positive, self-related stimuli and decreased for negative, self-related stimuli compared to baseline in MDD patients.[104] Moreover, improvements in depressive symptoms corresponded with the lower ventral ACC activity during negative self-referential processing.[104] These findings suggest that effective interventions for mood disorders may include decreasing negative self-beliefs, and the neural mechanism for these improvements is likely through self and regulation systems.

The exciting early work showing that MPFC activity is predictive of changes in health behaviors presents the self and regulation system as a prime candidate for studying the neural mechanisms for how interventions may change subsequent behavior. Here, behavioral interventions led to increased activity or connectivity in emotion and self-regulation regions that related to changes in health markers or outcomes, suggesting that increased self and regulation system activity may be one way behavioral interventions influence health. Another mechanism described was reduced self and regulation system activity to negative self-beliefs, which had important downstream health benefits as well. Thus, modulating activity in the self and regulation system is an important area of interest for future studies exploring links between interventions and health behaviors.

Discussion and future directions

Health neuroscience is a relatively new research domain,[105] and there is still much work to be done linking behavioral interventions to the brain and health. The initial studies we have reviewed here suggest that evaluating intervention effects for health, using a neurobiological systems approach, will help reveal how these interventions enact change and elucidate the biological mechanisms and cascades that drive health outcomes over time. In addition, manipulating behavioral processes can be quite informative. As the father of social psychology, Kurt Lewin, once said, “If you truly want to understand something, try to change it.”[106] Thus, interventions can be one tool for expanding knowledge on the associations between neural processes and health, and can provide information on the best intervention method for targeting the specific behavioral processes of interest. Specifically, by working to change behaviors, knowledge can be gained about the etiology and persistence of the behavior; similarly, by identifying mechanisms for interventions, the key components or boundary conditions of the intervention can be identified and lead to improvements in intervention delivery and efficacy. The work in this area has just begun, and future research should continue to investigate the health neuroscience of behavioral interventions, as there is significant value in moving toward causal models of health and behavior by manipulating the brain with interventions.

Our review (also see Tables 1–4) provides some initial promising indications for how behavioral interventions affect neurobiological systems and health. Quite a bit of research has pointed to stress as a potent detriment to health, and many behavioral interventions aim to reduce stress to improve health.[17] Decreased activity in the threat system following a CBT treatment for PTSD patients was associated with improvements in PTSD symptomatology.[66] Mindfulness intervention led to reductions in connectivity within this system in stressed adults, and this shift in connectivity was associated with reduced measures of cumulative activation of the HPA system.[67] Finally, mindfulness also led stressed adults to show enhanced connectivity within cognitive control regions, and this served as a mediator for reductions in inflammation.[72] This final study was one of the few to explicitly test neural changes as a mediator for biological health markers. However, it is still unclear exactly what these changes in connectivity mean or how they are associated with health outcomes. Considering the interest in stress reduction interventions, the threat system is still understudied. However, the work reviewed here shows that behavioral interventions can modulate the neural threat system in ways that influence stress and stress physiology, and future research can determine how these pathways may influence disease outcomes.

Chronic pain is a complex and difficult diagnosis and many pharmaceutical treatments are ineffective or produce side effects, leading to a recent increase in attention to behavioral interventions for pain. Here, we reviewed a few studies investigating the neural mechanisms of these interventions, two of which were conducted with chronic pain samples. Gut-directed hypnotherapy led to reduced pain system activity to pain stimulation for IBS patients, and exercise led to greater connectivity between nociception and pain regions for fibromyalgia patients, showing that behavioral interventions might alter how individuals respond to pain neurally.[80,83] In healthy adults without a chronic pain diagnosis, mindfulness training led to greater activity in cognitive control regions in response to pain stimulation, providing a foundation for future work exploring the effect of mindfulness interventions on chronic pain.[85] However, so far this work has not linked changes in neural activity or connectivity with changes in chronic pain symptoms for patients, an important avenue for future research.

Dysregulation in the neural reward system is linked to health conditions such as obesity and addiction.[87] Behavioral interventions that aim to change these health conditions would therefore logically target the reward system. Indeed, we reviewed work showing that various interventions reduced reward system activity to cues related to the health condition of study (i.e., food images for individuals with obesity).[93,94,96,107,108] Importantly, some of these studies found associations between changes in neural activity and important health markers. For example, after a weight loss intervention, decreased insula activity to high calorie food images was associated with more successful weight maintenance.[94] Behavioral interventions can reduce reward activity to unhealthy behaviors, but less work has yet examined how interventions might increase reward activity to healthy behaviors to reinforce them. Although there are some promising initial studies showing higher neural reward activity is linked to better health behavior,[13,98] future work can assess changes in neural reward activity from before to after treatment. In addition, it is not clear how long-lasting these effects are, with the obvious implication that the longer the effects persist, perhaps the more powerful the behavior change, particularly for those behaviors that are tenaciously difficult to modify (e.g., exercise). These studies provide a compelling foundation for future

behavioral intervention work that aims to adjust neural reward activity to change health behavior.

The self and regulation system is the most studied system in the health neuroscience of behavioral interventions, perhaps because behavioral interventions often aim to change how individuals cope with or regulate their behaviors and emotions—two essential roles of the self and regulation system. Critically, there is a body of work showing that the activity within this system is predictive of a variety of health behaviors, underscoring the value of interventions that affect this system.[55] For patients who completed CBT, greater activity in emotion regulation regions to pain stimulation was linked to changes in anxiety, an important symptom of fibromyalgia that can exacerbate disability.[102] In a population of MDD patients, CBT led to greater decreases in self and regulation system activity to negative information and parallel improvements in depressive symptoms.[104] Together, these results identify self-related processes as important contributors to health, and that interventions that help promote changes in neural activity underlying these processes may serve as a mechanism for health enhancement. Future work can provide a greater understanding of how behavioral interventions change activity within this system, how they are linked to behavior and affect, and, importantly, whether these changes are associated with improvements in health outcomes.

To date, most research has focused on examining how behavioral interventions alter brain function (and functional connectivity), while less research has evaluated how behavioral interventions impact brain structure. This is an exciting area, and some initial studies show experiences can affect brain structure (e.g., stress can increase amygdala volume), but also that some therapies and medications can alter brain structure as well.[109] It is reasonable to hypothesize that some behavioral interventions could change brain structure in ways that confer health benefits, and a few initial studies have explored this possibility.[110] Structural changes in the brain have been found to drive some functional effects in the brain as well,[26] therefore building out these structural-functional relationships when studying the health neuroscience of behavioral interventions is of value.

There are some methodological considerations in this new area of inquiry. First, much of the intervention research focuses on changes in neural activity and links to more proximal health outcomes (e.g., weight loss, anxiety, IL-6), but less work has been conducted linking intervention related changes in neural activity or connectivity with more distal health outcomes (e.g., diabetes, cardiovascular disease outcomes). Relatedly, most studies did not test changes in neural activity or connectivity as a statistical mediator of health, although there is some initial work adopting this approach.[72] New toolboxes and methods for conducting brain-based mediation analyses are now available for accelerating research in this area.[111] Additionally, as this area of study is still developing, it will be important to continue to replicate and extend these findings to related populations. A good example of this model is the work that explores the MPFC activity as a predictor for health behaviors; this effect has been replicated across a variety of studies, with varying health message formats and targeted health behaviors.[55,64,112] Indeed, converging, replicable evidence is still needed to fully identify the neural mechanisms of interest for health interventions.

Increasingly, patients are turning to behavioral interventions for helping manage some of their health concerns. Indeed, some patients are faced with potential medication side effects, treatments that only target the specific biological concern (i.e., chemotherapy targets the tumor but does not alleviate psychological distress from the cancer diagnosis), or health concerns that are marked by behaviors that are extremely difficult to change. Behavioral interventions may address some of these concerns, and importantly, can be used in combination with most pharmacological or procedural treatments. Health neuroscience has begun to explore the neural mechanisms that might underlie the health benefits of these behavioral interventions. Here, we have reviewed work that has explored how long-term behavioral interventions modulate neural activity in ways that lead to improvements in health outcomes. We organized these findings by the neural system intervention modulates, which helps to identify the target neural systems for future work. Indeed, this review suggests that interventions that are built to change stress physiology might reasonably look to connectivity within the threat system as a candidate system to affect. Although many of the interventions that found changes in neural pain system activity did not link this activity to a health outcome specifically, it is likely that modulating this system could lead to changes in how individuals perceive and respond to their pain, which could have important long-term benefits for chronic pain patients. If a behavioral intervention were intended to restructure the reinforcing nature of certain health behaviors, to reduce poor health behaviors or increase good health behaviors, the results we presented would point to the reward system as an important mechanism to explore. And finally, the self and regulation system appears to be an important marker of self-relevance and regulation success. Therefore, interventions that want to shift the individual's beliefs about their self or help them regulate their emotions and behaviors to be consistent with their view of self could reasonably hypothesize that the intervention should modulate self and regulation system activity. While the health neuroscience of behavioral interventions is still a young area of study, identifying the neural mechanisms that lead to changes in health has importance for a wide range of individuals interested in complementary treatments for their health. With increased knowledge of the neural mechanisms of behavioral interventions, more effective interventions can be developed. Future work on interventions can continue to explore theoretically sound possible neural mediators, investigate these patterns in clinical populations of interest, and link these neural mechanisms to relevant health markers and outcomes for maximum impact.

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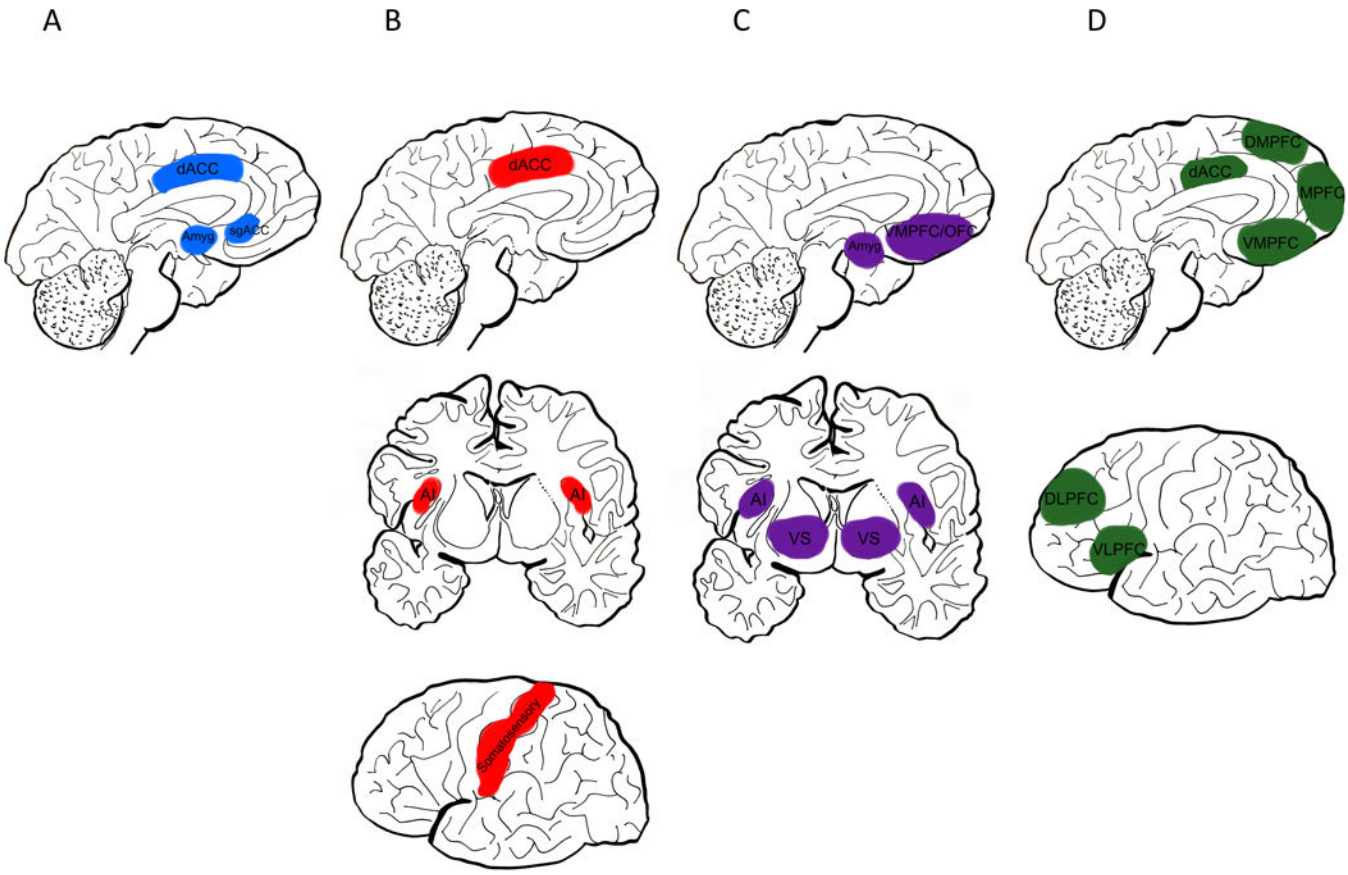

Figure 1.

Neural systems modulated by behavioral interventions. (A, B, C, D) Neural regions hypothesized to be part of the Threat and Stress System (blue, A), Pain System (red, B), Reward System (purple, C), and Self and Regulation System (green, D). Regions involved in threat and stress include the dorsal anterior cingulate cortex (dACC), amygdala (amyg), and subgenual anterior cingulate cortex (sgACC). Pain system regions include dACC (top), anterior insula (AI; middle), and somatosensory cortex (bottom). Regions involved in reward processing include the amygdala and ventromedial prefrontal cortex/orbitofrontal cortex (VMPFC, OFC; top) and the AI and ventral striatum (VS; bottom). Regions involved in the self and regulation system include the dACC, dorsomedial prefrontal cortex (DMPFC), medial prefrontal cortex (MPFC) and VMPFC (top), and the dorsolateral prefrontal cortex (DLPFC) and ventrolateral cortex (VLPFC; bottom).

Table 1.

Behavioral interventions and the threat and stress system

Study	Health condition of interest	Intervention	Population	Control group or condition	Task or analysis strategy	Findings	Link to health-relevant outcome
Felmingham *et al.*[66]	PTSD	Cognitive Behavioral Therapy (CBT)	PTSD patients	Baseline	Viewing threatening faces (threat reactivity task)	After CBT, patients showed greater sgACC activity compared to baseline, no change in amygdala activity	Increased sgACC activity correlated with a decrease in PTSD symptoms; decrease in amygdala activity correlated with decreased PTSD symptoms
Taren *et al.*[67]	Stress	3-day mindfulness meditation training retreat	Stressed adults	Relaxation retreat control group	Resting state connectivity	From baseline to after training, there was decreased amygdala-sgACC connectivity at rest compared to relaxation control	Decreased sgACC-amygdala connectivity at post-intervention was associated with HPA measures in hair samples (cumulative marker) for both groups
Creswell *et al.*[72]	Stress	3-day mindfulness training retreat	Stressed adults	Relaxation control retreat	Resting state connectivity	Meditation training increased connectivity between PCC and DLPFC compared to control	This increased connectivity between PCC and DLPFC meditated reductions in IL-6
King *et al.*[74]	PTSD	16-week mindfulness group therapy	PTSD patients	Present-centered group therapy	Resting state connectivity	Meidtation training increased connectivity between PCC and DLPFC compared to control	This increased connectivity between PCC and DLPFC was associated with PTSD symptom reductions

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Table 2.

Behavioral interventions and the pain system

Study	Health condition of interest	Intervention	Population	Control group or condition	Task or analysis strategy	Findings	Link to health-relevant outcome
Lowén *et al.*[80]	IBS pain	Gut-directed hypnotherapy	IBS patients	Educational intervention; healthy control subjects	High and low intensity rectal distensions	Patients that responded to hypnotherapy treatment showed reduced anterior insula activity to high intensity distension compared to baseline, and more of a decrease in anterior insula activity to low intensity distension compared to the education group	
Flodin *et al.*[83]	Pain	15-week exercise intervention	Fibromyalgia patients	Healthy controls	Resting state connectivity	At baseline: fibromyalgia patients showed decreased connectivity between pain and sensorimotor regions compared to controls. At post: patients showed greater connectivity between anterior insula and primary sensorimotor areas, looking more similar to controls	Not associated with changes in symptoms
Zeidan *et al.*[85]	Pain	4-day mindfulness training	Healthy adults		Heat pain stimulation	After mindfulness training, pain intensity rating reductions were associated with greater dACC and anterior insula activity, and reduced pain unpleasantness ratings associated with increased OFC activity compared to baseline	
Zeidan *et al.*[86]	Pain	4-day mindfulness training	Healthy adults	Sham mindfulness, placebo, book-listening control	Heat pain stimulation	Pain relief in the mindfulness group was associated with increased OFC, sgACC and anterior insula activity; placebo pain relief was associated with increases in DLPFC and somatosensory cortex activity; sham mindfulness pain relief was not associated with neural activity; no pain relief in control	

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Table 3.

Behavioral interventions and the reward system

Study	Health condition of interest	Intervention	Population	Control group or condition	Task or analysis strategy	Findings	Link to health-relevant outcome
Deckersbach *et al.*[93]	Obesity	6-month weight loss intervention	Obese or Overweight adults	Waitlist control group	Reactivity to high and low calorie foods	Intervention participants showed reduced VS activity to high vs. low calorie foods; the opposite was true for control subjects	No correlation between neural activity and weight loss
Murdaugh *et al.*[94]	Obesity	Weight loss intervention	Obese and overweight individuals	Normal weight controls	Reactivity to high and low calorie foods and neutral images	Compared to baseline, intervention subjects showed less MPFC to high-calorie food images	The more VS activity to high calorie foods at baseline, the less successful the weight loss; decreased insula activity at post compared to pre-intervention was associated with more successful weight maintenance
Cornier *et al.*[96]	Obesity	6-month walking intervention	Overweight or obese adults		Reactivity to highly rewarding food, neutral food and non-food images	After the intervention, participants showed reduced insula, visual cortex and parietal cortex activity to rewarding food images compared to baseline	Decreases in insula response to food cues was correlated with greater decreases in body weight and fat mass
Froeliger *et al.*[112]	Smoking	8-week mindfulness meditation-based intervention (MORE)	Smokers	No intervention	Reactivity to smoking cues, emotion regulation to smoking urges task	Following the mindfulness intervention, participants showed decreased VS and VMPFC activity to smoking cues, and increased VS and VMPFC activity to emotion regulation; results not shown in control group	Greater VS to emotion regulation was associated with reductions in smoking and urges to smoke
Feldstein Ewing *et al.*[108]	Substance abuse	Motivational interviewing	Adults with alcohol dependence		Viewing statements consistent with change (change talk)and statements inconsistent with change (counterchange talk)	Increased OFC, insula and VS activity to an alcohol cue following counterchange talk statements, but not following change talk statements	

Table 4.

Behavioral interventions and the self and regulation system

Study	Health condition of interest	Intervention	Population	Control group or condition	Task or analysis strategy	Findings	Link to health-relevant outcome
Falk et al.[55]	Sunscreen use	Sunscreen use messages	Young adults		Viewing ads about the importance of sunscreen use		Greater MPFC activity to sunscreen use messages was associated with greater sunscreen use at follow-up
Falk et al.[64]	Smoking	Smoking cessation messages	Smokers		Viewing smoking cessation messages		Greater MPFC activity to smoking cessation messages was associated with reductions in smoking behavior
Cooper et al.[98]	Smoking	Smoking cessation messages	Smokers		Smoking cessation messages or self-judgments task		Greater MPFC to smoking cessation ads was associated with reduced smoking behavior, but MPFC activity to self-judgments task was not
Chua *et al.*[99]	Smoking	Smoking cessation messages	Smokers		Viewing tailored anti-smoking messages or less tailored anti-smoking messages (control)	Tailored anti-smoking messages led to greater MPFC and precuneus activity compared to more generic messages	
Falk *et al.*[100]	Physical activity	Self-affirmation	Young adults	Control condition	Messages to encourage physical activity	Those in self-affirmation condition showed greater VMPFC activity to physical activity messages than control participants	Greater VMPFC activity to physical activity messages in self-affirmation group was associated with increased physical activity
Jensen *et al.*[102]	Pain	Cognitive Behavioral Therapy	Fibromyalgia patients	Fibromyalgia patients in waitlist control group	Pressure Pain Stimulation	After CBT, patients showed increased VLPFC activity to pressure pain compared to baseline, but not the control group; CBT patients showed an increase in VLPFC-thalamus functional connectivity after treatment, but there was no change in the control group	Correlation between increases in VLPFC activity correlated with decreases in anxiety
Yoshimura *et al.*[104]	Depression	Cognitive Behavioral Therapy (CBT)	Patients with major depressive disorder	No therapy in patients without depression	Self-judgments of descriptive words (positive and negative)	At baseline, MDD patients showed greater MPFC during self-referential processing of negative words compared to	Lower pACC activity during processing of negative words corresponded with

Study	Health condition of interest	Intervention	Population	Control group or condition	Task or analysis strategy	Findings	Link to health-relevant outcome
						controls; after CBT, MDD patients showed greater MPFC and pACC activity to positive words, and decreased activity for negative words	improvements in depressive symptoms
Riddle *et al.*[113]	Smoking	Graphic health warning labels on cigarettes	Smokers		Graphic health warning labels on cigarettes	Increased VMPFC to warning labels compared to control	Increased VMPFC and amygdala activity to labels effectively predicted reductions in smoking behavior
Tang *et al.*[114]	Smoking	Two-week meditation training	Smokers and Non-smokers	Relaxation training control; non-smokers	Resting state activity	At pre-intervention, smokers showed less resting state dACC and left VLPFC activity than non-smokers; smokers in mindfulness group showed increased dACC, MPFC and VLPFC activity compared to baseline, and no significant change in control group	
Goldin, Ziv, Jazaieri, Hahn & Gross[115]	Social anxiety disorder	Mindfulness-based stress reduction	Patients with social anxiety disorder	Aerobic exercise	Self-belief statements	After MBSR, compared to exercise, participants had decreased right VLPFC activity to viewing statements about their negative self-beliefs	
Goldin, Ziv, Jazaieri & Gross[116]	Social anxiety disorder	Mindfulness-based stress reductions	Patients with social anxiety disorder	Aerobic exercise	Determining if negative and positive trait words and decided if they describe them or if they have a capital letter (control)	Compared to baseline, MBSR led to increased VMPFC activity to self-judging negative words, but not for the exercise group	Increased activity in DMPFC to self-endorsement of negative words (compared to capital letter judgments) for MBSR participants, but not for exercise participants, was associated with decreased social anxiety disorder symptoms
Ritchey *et al.*[117]	Depression	Cognitive Behavioral Therapy (CBT)	Patients with major depressive disorder	No therapy in patients without depression	Positive, neutral and negative images	After treatment, MDD patients showed an overall increase in VMPFC activity; a larger increase from baseline in right amygdala, right caudate and left hippocampus activity for emotional compared to neutral images	Higher baseline VMPFC was associated with greater MDD symptom resolution after CBT
McFadden *et al.*[118]	Obesity	6-month walking intervention	Overweight adults		Resting State Activity	After the intervention, participants showed decreased activity in precuneus	Decreases in precuneus activity were correlated with reductions in fat mass and hunger