Anxiety and Brain Networks of Emotion and Attentional Control[1]

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ABSTRACT

The inability to control thoughts, images and urges related to perceived threat marks a variety of disorders, including generalized anxiety disorder, phobias, social anxiety disorder, separation anxiety, post traumatic anxiety disorder and obsessive compulsive disorder. In this paper we summarize literature that links anxiety disorders to brain networks of emotion and attentional control. Following the outline of NIMH Research Domain Criteria (RDoC) we seek to define these disorders in terms of neural networks of negative affect and self-regulation and to view remediation as improved network performance.

Key words
Alerting Network, Anxiety, Attention, Fear, Orienting Network, Executive Network, Startle

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1. Introduction

Anxiety is an emotional state characterized by the subjectively unpleasant experience of dread over anticipated events. Anxiety is normal, even necessary in order to avoid dangers or threatening stimuli. However, undue anxiety can be debilitating for the individual and for society. Anxiety disorders include generalized anxiety disorder (GAD), post-traumatic distress disorder (PTSD), phobias, and social anxiety disorder(SAD). Although obsessive-compulsive disorder (OCD) has been excluded from the list of anxiety disorders in the newest classification of mental disorders, anxiety has been identified as one of its core elements (DSM-5,2013). Our recent review of the OCD literature (Ghassemzadeh, Rothbart, & Posner, 2017) identifies anxiety as central to its treatment and we include it as a part of this paper.

The goal of this paper is to further understanding of the common neural networks involved in anxiety and its disorders. To foster this goal, it is important to review some of the recent history of thinking about anxiety. Anxiety disorders have been reported as the most common mental health problem in the United States. It has been estimated 40 million adults in the US currently have an anxiety disorder (18% of population; 12-month prevalence; NIMH, 2013). There has been a distinction between fear and anxiety in relation to clinical evaluations. While fear is defined as “the emotional response to real or perceived threat”, anxiety has been indicated as “anticipation of future threat” (APA, 2013, p.189). In the animal literature, fear to predictable events is differentiated from sustained unpredictable fear (with the latter labeled anxiety) (Davis,Walker, Miles, & Grillon; 2010).

At the start of the 21st century in a special issue of the *Psychiatric Annals* devoted to anxiety disorders (Simon &Pollack, 2000), the editors stated that "the goal of treatment has shifted away from symptom reduction alone and toward a more theoretical approach based upon understanding fear and anxiety in the human brain" (p.676). After17 years, steps have been taken toward a more theoretical approach but it has become evident that we need a more reliable and promising classification system as well as approaches to treatment based on an understanding of the mechanisms of anxiety.

The NIMH Research Domain Criterion (RDoC) was formulated to foster the theoretical understanding of mechanisms of anxiety and other forms of psychopathology (Insel et al., 2010; 2014), with the goal of freeing investigators from the boundaries of symptom-based categories. As a framework for organizing research the RDoC project defined five domains (Insel et al., 2014). Two of these, positive and negative valence, are related to brain networks underlying emotion, although recent research suggests that the brain represents primary emotions in more differentiated and separable networks. Three of the RDoC domains are associated with modulatory mechanisms involving cognitive, social and arousal systems. We view these domains as related to the mechanisms of attention and self- regulation discussed in this paper.

2. Attention in Anxiety disorders

Early cognitive models viewed anxiety disorders in terms of a biased or selective information processing system (Beck, 1967, 1976; Beck, Emery, & Greenberg, 1985; Clark & Beck, 2010). The basic assumption was that dysregulation of cognition in anxiety disorders is developed and maintained by attention to memories relevant to anxiety (Clark & Beck, 1999; Gotlib & Neubauer, 2000).

When attention was viewed as a single process and little was known about the neural mechanisms involved, dysregulation of attention implied very little about the diagnosis or potential remediation of disorders related to it. It is now generally understood, however, that attention refers to a number of different functions and brain networks (Corbetta & Shulman, 2002; Petersen & Posner, 2012; Posner & Petersen 1990; Trofimova & Robbins, 2016). The idea of brain networks related to psychological functions goes back at least to Hebb (1949), but has received more emphasis since neural imaging has shown that many human tasks are orchestrated by a number of widely separate brain areas and their connections (Corbetta & Shulman, 2002; Posner & Raichle, 1994).

To understand how a neural network approach might improve our understanding, we first consider the RDoC's definitions of attention and cognitive control (Insel, 2013; Insel et al., 2010). Attention is defined as processes of selection and divided attention, with no discussion of its relation to brain networks. Cognitive control is defined as "a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior". Both of these definitions are functional, with no effort to link the definitions to brain networks.

This paper reviews neural networks related to attention and negative emotion as a way of establishing greater contact with the goal of NIMH to view psychopathology in biological terms (RDoC, see Insel, 2013). Several recent papers have used a network approach to anxiety and depression (Lang, McTeague, & Bradley, 2016; McTeague & Lang, 2012; Williams et al., 2016; Woody & Gibb, 2015). The use of heart rate and startle responses to fear-related imagery, for example, has shown involuntary attention to fear- related probes (Lang, McTeague, & Bradley, 2016), providing an important approach to understanding the physiological basis of anxiety responses (Lang, McTeague, & Bradley, 2016).

We extend this work by examining recent findings related to how emotion is expressed in the brain and how both voluntary and involuntary attention networks can be used to moderate negative affect. In this paper we first review attention networks in relation to anxiety and the anxiety disorders. We then examine studies of networks related to negative emotion. Finally, we consider the consequences of attention and emotion networks for research into therapies designed to reduce anxiety.

3. Networks involved in attention

Attention refers to a system of cognitive functions that allow the brain to prioritize particular stimuli for dedicated processing. Prioritizing is essential because one's cognitive capacity is limited (Petersen & Posner, 2012). Moreover, rapid responses to threatening stimuli may be critical to the organism's survival.

Three networks have been recognized as related to different aspects of attention. These include alerting, orienting, and executive attention (Petersen & Posner, 2012; Posner & Petersen, 1990; Posner & Rothbart, 2007). Each network has been identified with a specific neuromodulator, and candidate gene studies have identified specific genes associated with the different networks (see Posner, Rothbart, Sheese, & Voelker, 2014 for review). The Attention Network Test (ANT) has been used to measure individual differences in these networks. The task involves presentation of a target arrow; the participant's task is to press a key corresponding to the arrow's direction. On conflict trials the target arrow is surrounded by arrows pointing in the opposite direction. By subtracting RTs to arrows in the same direction from those in the opposite direction, one gets a measure of the time to resolve conflict, a defining feature of the executive network. The test also involves cues as to when and where the target will occur that allow measurement of individual differences in the alerting and orienting networks (Fan et al., 2002).

3.1. Alerting

Alerting is a state in which the organism shows heightened sensitivity to incoming stimuli. This state, when induced by a warning signal, involves slowing of heart rate and a general inhibition of reflex responses, including the startle response. The brain regions involved in this state include the brain's norepinephrine pathway, including the sub-cortical locus coeruleus as well as frontal and parietal regions of the cortex (Petersen & Posner, 2012).

In the approach of cognitive psychology toward research on alerting, a major emphasis has been on producing and maintaining optimal vigilance and performance during tasks. Both classical lesion data and more recent imaging data confirm that tonic alertness is heavily lateralized to the right hemisphere, while phasic alerting, as in alerting following a warning signal appears to rely more on left hemisphere brain areas (Coul, Frith, Buchel, & Nobre, 2000).

Alerting has been shown to be related to activity in the locus coruleus, the source of the brain's norepinepherine system. A recent mouse study, however, found that activation of locus coeruleus neurons connected to the amygdala can also produce anxiety states (McCall et al., 2017). Davis et al. (2010) suggest that in humans, symptoms of clinical anxiety are better detected in sustained rather than phasic fear paradigms. Since the link between alerting and anxiety could result from the heterogeneous nature of locus coeruleus connections (Chandler, Gao, & Waterhouse, 2014), it is important to determine the conditions under which the two are related.

3.2. Orienting

The orienting function deals with the ability to prioritize sensory input. In experimental studies a cue is used to direct orienting to a location (Posner, 1980). Cortical areas involved in orienting include the superior parietal cortex and temporal parietal junction, as well as the frontal eye fields. The functions of the parietal lobe are not restricted to sensory stimuli but may involve other related processes such as disengaging from memories.

Subcortical areas include the pulvinar and superior colliculus. Lesions of the superior temporal lobe and temporal parietal junction have been consistently related to difficulties in orienting to the side of space opposite the lesion (Karnath et al., 2001). In experimental studies, the temporal-parietal junction is activated when disengaging from a target in order to reorient attention (Corbetta & Shulman, 2002).

Orienting has been widely studied in the anxiety disorders. LeDoux and his colleagues (LeDoux, 1998; LeDoux, Sakaguch, & Reis, 1984) were among the first to describe the neural circuitry of orienting to auditory threats in rodents. Three components of threat related orienting were identified: 1) a rapid response that encodes relatively crude details concerning the nature of threat. This early response primarily involves the amygdala; 2) a set of processes that develop slowly and encode more detailed information about the threat. This aspect of orienting is mediated by cortical regions involved in the relevant sensory modalities; and 3) the behavioral component, which is mediated by prefrontal cortex (PFC).

Studies of cueing have suggested that anxiety chiefly affects the ability to disengage from a cue rather than the speed of orienting toward the cue (Fox, Russo, Bowles, & Dutton, 2001). This finding may allow additional time for executive attention to become involved in the decision. Although older data suggested independence between the two networks, more recent data ~~suggests~~ shows that orienting and executive networks may have a common bottleneck under conditions of simultaneous demands (Trautwein,Singer, & Kanske, 2016) thus, in addition to orienting, executive attention (discussed further below) exerted toward an emotional stimulus could be important in its influence, particularly on expected threats (Sarapas et al., 2017).

3.3. Executive Attention

Executive attention involves the control of voluntary responses toward implementing a person's current goals and is responsible for resolving conflicts that occur between different brain computations (Petersen & Posner, 2012). This function is most often assessed by tasks such as the Flanker or Stroop task that involve the resolution of conflict. The more efficient the executive network is the less time will be required to resolve conflict.

Resolving conflict in these tasks activates midline frontal areas (anterior cingulate) and medial prefrontal cortex, insula and underlying striatum (Fan et al., 2005; Posner and Rothbart, 2007). This network largely overlaps with the cingulo-opercular network described in fMRI studies of control (Dosenbach et al., 2007).

Substantial research has shown that time to resolve conflict is related to the ability of children and adult to regulate or control their voluntary responding (Posner & Rothbart, 2007). Various forms of psychopathology including schizophrenia, borderline personality disorder, and Attention Deficit Disorder have been found to have very high conflict scores.

Within the anterior cingulate cortex, networks for emotional and cognitive control involve both separate (Beckmann, Johansen-Berg, & Rushworth, 2009; Bush, Luu, & Posner, 2000) and overlapping areas (Smith et al., 2009). Control of both negative and positive emotions has been found to activate this network when people are asked to modify or control their reaction to negative pictures and words.

4. Individual Differences

Brain networks of attention are common to all people but their efficiency differs among individuals (Fan et al., 2002). In part, these differences involve genetic variations in interaction with environmental factors (Posner et al., 2014). We have shown that individual differences in the efficiency of each network are influenced by genetic polymorphisms related to the networks dominant neuromodulators (Posner et al., 2014 see also Table 1). This approach may further our understanding of the susceptibility of individuals to anxiety disorders and the response to the treatments discussed in the final section of this paper.

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Studies of human temperament using parent report questionnaires have consistently shown that attentional control is negatively related to negative affect (Rothbart, 2011). This has led to the idea that attention through its control of emotion can reduce the influence of negative affect on behavior (Posner & Rothbart, 2007; Rothbart & Sheese, 2007).

Recent human studies of individual differences have been based on a series of animal experiments (Davis et al., 2010). Using measures of fear potentiated startle, Davis and colleagues empirically distinguished fear to predictable events (labeled fear) from sustained fear to unpredictable events (labeled anxiety). A study with a large sample of undergraduates (Sarapas, Weinberg, Langmeyer, & Shankman, 2017), revealed important links between individual differences in proneness to anxiety and attention. This study used the ANT, which measures individual differences in each of the networks related to attention, and questionnaires to measure trait and state anxiety, as well as startle responses to expected and unexpected events. The study found higher startle to unexpected threats to be correlated with faster alerting and slower disengaging of orienting from cued locations as measured by the ANT. However, high startle to expected threat was correlated with poorer executive attention as measured by high conflict scores in the ANT.

The Sarpas et al. (2017) study is correlational, thus leaving unclear whether the attention networks are the cause of increased startle. Although recent rodent data (McCall et al., 2017) has shown that the locus coeruleus activity can cause both alerting and anxiety, whether they do so by the same or different pathways is still unclear. However, a new comparative approach (Lovett-Barron et al., 2017) to the study of alerting has identified the cell types involved in alerting in diverse organisms, and may allow further studies on relations between the alert state and anxiety. This approach could also help to determine which aspects of fear and anxiety as found in various animal paradigms are related to different forms of human psychopathology (Davis et al., 2010).

5. Fear and negative emotion circuits

In a review article, Bishop (2007) concludes that there is “strong support for a common amygdala-prefrontal circuitry underlying selective attention to threat, interpretation of stimuli, and acquisition and extinction of conditioned fear” (pp.314-315). Bishop considers heightened amygdala activity and reduced prefrontal recruitment as responsible for biasing the organism toward threat-related responses. In one study, faces displaying negative affect were shown to 22 patients diagnosed with General Affect Disorder / SAD (Robinson et al., 2014) during brain imaging. The patients activated a circuit involving the anterior cingulate/mid prefrontal cortex and amygdala more strongly than the controls. This circuit may involve attempted control of the negative emotion indicated by the facial expression.

Understanding how emotion is represented in the brain is important to determining the brain networks controlled by attention. One recent study (Williams et al., 2016) has argued for a single negative affect circuit responsible for representing all negative emotionality. Until recently, however, imaging techniques such as

MRI were not successful in activating the underlying neural circuits of the separate negative emotions.

Employing a newly developed multivoxel pattern analysis method, Kragel and LaBar (2016) have begun to separate neural activations involved in primary negative emotions such as disgust, fear, sadness and anger and positive ones such as happiness and surprise. In a study using both music and film clips to arouse the emotions, they found widespread cortical and subcortical differentiation of activation for each of six primary emotions. Each emotion activated different but somewhat overlapping neural areas. These findings were confirmed by resting state observations of similar brain network activation, which were correlated with subjective reports of the feelings of the participants (Kragel, Knodt, Hariri, & LaBar, 2016). These correlations were largest when computed from non- overlapping areas of activation, suggesting the importance of unique brain areas in the processing of emotion.

The ability to predict spontaneous reports of emotions during resting state from the brain areas active during sensory stimulation further supports the involvement of the primary emotions. While the primary emotions could be detected in these activation patterns, less ability to predict feelings was found for a classification based on valence and arousal strength, suggesting that those broad dimensions were not the primary basis for brain activity representing emotions.

In a study of emotions induced by short movies, a number of brain areas separated by valence were activated, including the orbital frontal cortex but also including posterior areas of the precuneus and posterior cingulate (Saarimaki et al., 2016). The orbital frontal cortex also showed evidence of separating positive from negative valence when stimuli were presented either by vision or by smell (Kragel & La Bar, 2016). The accuracy of classification by valence in this area, though significant, was not very high, again suggesting somewhat separate representation for each of the primary negative emotions.

The difficulty of separating the valence of emotion by MRI may be due to different emotions activating separate neurons within the same brain area. Recent work in mice has shown a distinction within the basolateral amygdala complex between the two valences. Within this structure, separate neurons are activated by positive reinforcement and punishment, with reward related to the nucleus accumbens and punishment to the central medial amygdala (Namburi et al., 2015). Research with humans also reveals activation of the amygdala for both positive and negative primary emotions; however, each emotion reveals a different set of connected areas in addition to the amygdala (Diano et al., 2017).

Although it has been suggested that learning plays an important role in threat detection, humans also possess pathways by which attention can be brought quickly to some evolutionary threatening stimuli such as snakes and spiders. This type of evolutionary bias toward relevant threat stimuli, which can be seen in young children, should be taken into consideration in research on the systems supporting anxiety and fear (Lobue & Deloache, 2008; Lobue, Rakinson & DeLeoache, 2011).

Because evidence suggests some separate brain areas for each emotion there is the possibility that each negative emotion has its own link to medial frontal control mechanisms. It is unclear whether all negative affects can be controlled together by suppressing negatively valenced emotions as a whole.

6. Attention Bias

The term attention bias refers to preferential processing of material that has disorder-relevant emotional meaning (Mathews & MacLeod, 2005). Such a bias would provide preferential orienting toward and awareness of the negative emotions related to the person’s disorder. The study of attention biases appears particularly pertinent for how therapies might suppress privileged access of content related to the disorder (Ghassemzadeh et al., 2017; MacLeod &Mathews, 2012; McNally, 2007).

6.1. Tasks Demonstrating Bias

A review paper has summarized work to determine the mechanisms of attentional bias in anxiety disorders (Cisler & Koster, 2010). The paper considers four experimental paradigms used to measure attention bias in anxiety: 1) the emotional Stroop task; 2) dot-probe tasks 3) visual search; and 4) spatial attention tasks. The original Stroop task was introduced in 1935 to study attention in all people (Stroop, 1935). In this task, the participant is required to name the color of a word while ignoring the word itself (for example, a word such as RED might appear in Green color and the participant is expected to name the color- green- rather than the word red). This conflict is resolved by the executive attention network and the extra time required to respond to incongruent color and word names is a measure of the efficiency of this network. Numerous studies have demonstrated that clinically anxious participants show a disproportionate amount of slowing to color when the words are emotionally threatening compared to neutral words, suggesting that the words produce greater attention in the patients than in controls and that this increased attention to threat interferes with the processing of color (see Williams, Mathews, & MacLeod, 1996, for review). The additional Stroop interference with threat-related words found by Williams et al. indicates the role of executive attention in aspects of attention bias.

Whereas the emotional Stroop task is linked to the executive attention network, Cistler and Koster's (2010) next three tasks are more closely related to the orienting network. The dot-probe task is a second measure of attentional bias (MacLeod et al., 1986). In this task individuals respond to a probe that replaces a threat-related or neutral word on a screen. It is expected that individuals oriented to threat will respond more quickly to probes replacing threatening words than those replacing neutral words. When the dot probe task was modified by comparing detection (i.e., determining whether there is a probe) with determining the type of probe, the authors were able to separate orienting toward the threat word versus disengagement from the threat, and found that it is disengaging that is delayed in fearful subjects. (Salemink,van den Hout, & Kindt, 2007).

A third very general method uses visual search of a complex array of stimuli. In this method one can examine the time to orient to a negative stimulus related to a person's phobia. A study by Ohman, Flykt, and Esteves (2001) showed greater efficiency in orienting toward a feared stimulus, but did not provide specificity as to the underlying operations. However, a fourth method closely related to visual search is the spatial attention task (Posner, 1980; Fox, 2004), which involves the orienting network. When performed rapidly, this task allows separation of attention toward a negative object from disengaging from the negative object.

There is strong evidence that attentional bias to threat involves difficulty in disengaging from the threatening stimulus (Cisler & Koster, 2010). This is found particularly in the spatial attention task, but also in other relevant tasks. Most of these studies involve non-clinical samples showing high trait anxiety (Fox et al., 2001). When patients diagnosed as having GAD performed this task, however, they showed faster disengagement and were slower to engage the negative stimulus than non-patient controls, as though they generally avoided the fearful stimulus. The non-clinical sample was much younger and faster than the patients and their controls, and the patient study may have involved more deliberation and drawn more heavily on the executive network, as might be expected when threat words were expected. To investigate this possibility, it would be important to carry out the spatial conflict task with fMRI to study the attention networks involved.

6.2. Disengagement

Imaging studies that can reveal the attention network involved are important because imaging has shown that disengaging from an invalid stimulus in the spatial attention task involves a problem with the right temporal parietal junction (Corbetta & Shulman, 2002), a possible brain basis for the disengage difficulty when the orienting network is involved. Deweese and associates (Deweese et al., 2014) used EEG to show that pictures related to snakes produced a larger sustained interference with processing a non-snake target for those suffering from snake phobias than for controls, as though those with snake phobia had difficulty breaking orienting to the snake even when the pictures were irrelevant to the task of detecting targets. Moreover, sustained orienting to threat likely also activates the executive attention network, which is in turn influenced by the person's goals. The involvement of executive attention fits with increased Stroop interference to threat for those with high trait anxiety and also for conflicting findings in a number of paradigms about the extent to which threat facilitates voluntary attention or leads to avoidance of the threatening object by anxious individuals (Cisler & Koster, 2010; Goodwin,Yiend, & Hirsch, 2017). A major issue here is whether the threat is expected or unexpected (Sarapas et al., 2017).

In a meta- analysis by Bar-Haim et al. (2007) of 172 published studies comparing patients to non-patients in bias to attend to threatening stimuli, results favored greater bias in trait anxious patients, although the nature and mechanism of this bias was uncertain. The network approach we have been discussing provides a possible perspective on the mechanisms involved. It seems likely that the orienting network, particularly the temporal parietal junction, is important in the difficulty of anxious individuals in disengaging from a threatening stimulus, especially when the threat is unexpected, while the executive network, including the anterior cingulate and insula, is involved when people with anxiety disorders consciously attend to threatening information, particularly when the threat is expected (Muller & Roberts, 2005; Sarapas et al., 2017). Resting state studies of patients with GAD show that in comparison with controls there is evidence of a functional deficit in the left ACC and several other brain areas (Xia et al., 2017). This might imply difficulty in conscious control of emotional states.

The underlying process of attentional bias seems to be that anxiety reduces the ability to disengage from unexpected threat by the orienting network, and may also increase sustained involvement with threatening material. Voluntary attention may lead the person to either sustain attention to the threat or to switch from it, depending upon their current goals. We speculate that undergraduate participants rely more on the automatic orienting network when dealing with threat, while older patient population may rely more on the executive network and thus show less consistent results.

7. The role of attention in treatment

An important approach relating the neural circuits of attention to anxiety disorders is attention control theory (Barry, Vervliet, & Hermans, 2015; Eysenck, Derakshan, Santos, & Calvo, 2007). The central notion of this view is that anxiety and its disorders decrease the influence of the executive attention network in carrying out the person's goals and also lead to the failure of the orienting network to disengage from stimuli related to anxiety. The distinction between the orienting and executive network differs from the idea of Williams et al. (2016) of a single attentional control network. We have outlined above the substantial developments in the imaging of negative emotion networks, the crucial sites on which attentional control operates.

According to the view discussed in this paper, pathologies related to anxiety can emerge through over-activity in the negative emotion networks or from inability to disengage from negative ideas because of problems in the attention networks (Eysenck et al., 2007). A recent MRI study comparing patients with GAD with controls supports both areas being important in their finding that patients compared with controls have greater activity in both emotional and regulatory areas (Fitzgerald et al., 2017).

The idea that both regulatory and emotion areas are involved in disorders presents an opportunity to propose possible improvements in treatment of anxiety disorders based on our understanding of the attention networks. Accepting that biased orienting serves to maintain high anxiety, treatments that alter attentional orienting should alleviate anxiety. The bulk of the evidence is that people with high anxiety have difficulty orienting away from negative affect. This would involve primarily the right temporal parietal junction, identified as the major structure involved in disengaging from a target (Corbetta & Shulman, 2002).

One approach to modification of attention is training on specific cognitive tasks (Tang & Posner, 2009). Attention Bias Modification Therapy (ABMT) is one of these procedures. Most studies use the dot-probe task as a therapeutic tool. During training, the target location is systematically related to either the neutral or negative image or word. Training attention involves practice in moving attention away from negative stimuli (McLeod & Matthews, 2012). In some cases such training reduced anxiety symptoms up to four months after training (Schmidt et al., 2009); however, meta-analysis of many studies using only ABMT training methods have shown more modest gains (Liu et al., 2017).

Cognitive bias modification (CBM) is a more general approach to modifying anxiety that targets the executive network as well as the orienting network (McLeod & Matthews, 2012). One version targets shifting away from negative memories or instructs the person to reframe negative ideas as not involving weakness or failure to cope, but instead as evidence of positive coping (MacLeod & Mathews, 2012). These methods have generally proven more effective than ABMT training alone (Liu et al., 2017), but unlike attention training, little is known about the brain mechanisms involved.

An approach providing more information about mechanism is training to improve implementation of goal directed behavior that might inhibit activation of the negative affect networks (Tang & Posner, 2009). A likely target for such therapy would be improved ACC or insula input into the amygdala. In a study of 45 normal subjects under threat of shock, an instruction to move attention away from a threatening stimulus to a neutral stimulus reduced the functional connectivity in this network (Robinson et al., 2016).

There have also been several recent efforts to improve brain networks of cognitive and emotional control. Studies of mindfulness meditation have shown a clear reduction of negative mood in normal volunteers following 5 to 20 sessions (Tang et al., 2007; 2009). Meditation training compared to a relaxation training control led to greater activation of the anterior cingulate and improved white matter connections surrounding the ACC as measured by Diffusion Tensor Imaging. These include inputs to the limbic system in general and the amygdala in particular (Tang et al; 2010; 2012). One of the effects of meditation training is also to increase EEG theta rhythm in the frontal lobe (Xu et al., 2014).

Recently Weible et al. (2017) induced theta rhythm in the anterior cingulate cortex of mice. A month of half hour sessions of rhythmic stimulation at 8 Hz was found to reduce anxiety in the mice as revealed by the increased amount of time they spent in the light part of their chamber compared with unstimulated controls. Time spent in the light is usually found to be correlated with reduced fear or anxiety. In addition, the same authors found an increase in white matter near the ACC as measured by electron microscopy (Piscopo et al., in process). Of course, mice are not humans, but there are some indications that similar networks may be influenced in the human brain. Human studies have used DC stimulation across the frontal lobes to enhance learning (Krause & Cohen-Kadosh, 2013; Parasuraman & McKinley, 2014), and such stimulation can enhance intrinsic theta activity in midline areas, possibly similar to the mechanism observed in the mouse stimulation studies (Reinhart, Zhu, Park, & Woodman, 2015). Another recent paper (Reinhart, 2017) in humans found that synchronizing theta rhythms in the ACC with those in the lateral frontal areas can enhance executive control. This is strong evidence suggesting that frontal theta may have similar effects in humans as in mice.

A study of people recruited to control stress found that smokers trained with two weeks of meditation training reduced their smoking following training as assessed objectively, often without being aware that they had done so. The underlying connectivity between the ACC and striatum was, however, enhanced. This provides some evidence for increased control by changing the network following meditation training, even without the person having a goal to reduce their addiction or even being aware that they had done so (Tang, Posner, Rothbart, & Volkow, 2016).

While these results suggest that improvement in the underlying network by which executive attention controls negative emotion provides an important therapeutic approach, it is not clear whether enhancing the executive network will always serve to reduce the bias toward negative affect found in anxiety disorders. For example, in searching for a common underlying mechanism in GAD and OCD, Armstrong, Zald and Olatunji (2011) examined deficits in attentional control as a cognitive vulnerability that may contribute to both obsessional thoughts and perseverative worry. They found that low attentional control was related to obsessive thoughts but only in the GAD group, implying that obsessional thoughts may not always be related to attentional control. The differing results between GAD and OCD in this study suggest that different forms of anxiety may involve attention in different forms, requiring different treatments. For example, in the Tang et al. (2007) study, attentional control may have increased emotion regulation, leading to reduced anxiety in non-patient undergraduates, but generalized attention training may not be as helpful in OCD patients.

Clearly there are many unanswered issues in attempting to use the present neuroscience findings to design therapeutic methods. For example, we do not know exactly which animal paradigms involving fear or anxiety are related to psychopathology in humans. Nor are we sure that paradigms involving high anxiety in typically developing undergraduates will predict who will later show evidence of an anxiety disorder. However, there now appears to be sufficient evidence to carry out the needed research with the various anxiety related disorders.

8. Summary

The new approach to diagnosis and treatment of mental illness fostered by NIMH (RDoC) places emphasis on disorders of brain networks that are related to genetic variability and pathology. Our paper examined anxiety in these terms. We discussed brain networks of attention that serve as the control networks in self- regulation, allowing disengaging from negative emotion networks. We also discussed brain networks involved in fear and other primary negative emotions. According to our view, pathologies of anxiety may emerge either through overactivity in the emotion affect networks or from the inability to disengage from negative ideas because of problems in attention networks. Research is needed to determine whether therapies based on these principles may be useful in those suffering from anxiety disorders.

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