Neural systems underlying approach and avoidance in anxiety disorders

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Approach-avoidance conflict is an important psychological concept that has been used extensively to better understand cognition and emotion. This review focuses on neural systems involved in approach, avoidance, and conflict decision making, and how these systems overlap with implicated neural substrates of anxiety disorders. In particular, the role of amygdala, insula, ventral striatal, and prefrontal regions are discussed with respect to approach and avoidance behaviors. Three specific hypotheses underlying the dysfunction in anxiety disorders are proposed, including: (i) over-representation of avoidance valuation related to limbic overactivation; (ii) under- or over-representation of approach valuation related to attenuated or exaggerated striatal activation respectively; and (iii) insufficient integration and arbitration of approach and avoidance valuations related to attenuated orbitofrontal cortex activation. These dysfunctions can be examined experimentally using versions of existing decision-making paradigms, but may also require new translational and innovative approaches to probe approach-avoidance conflict and related neural systems in anxiety disorders.

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"Conflict" occurs when a person or animal is faced with opposing drives, ie, incentives to act, that are incompatible with one another.[1-3] For example, conflict can be instigated when the same action is associated with both reward and punishment, as in the case of approach-avoidance conflict, or when two distinct actions are associated with somewhat balanced rewards (approach-approach conflict) or punishments (avoidance-avoidance conflict). Conflict poses a unique challenge for comparing the value of available options in a decision-making situation. Individuals must integrate a variety of information concerning the value of potential rewards and punishments, and the likelihood and magnitude of those potential outcomes.[4]

Conflict between opposing internal or external drives was recognized as an important process for understanding psychopathology as early as the 1900s. Conflict was conceptualized in unique ways by two ancestral lines of psychology—psychoanalytical thought led by Sigmund Freud,[5] and behavioral psychology led by Ivan Pavlov.[6] Although these two fields used disparate experimental approaches, the similarities between Freud's concept of psychic conflict and Pavlov's use of conflicting conditioned reflexes to produce "experimental neuroses" were soon recognized.[7,8] Since that time, various experimental methods, paradigms, and self-report measures

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Selected abbreviations and acronyms

ACC	*anterior cingulate cortex*
GAD	*generalized anxiety disorder*
OFC	*orbitofrontal cortex*
PFC	*prefrontal cortex*
PTSD	*post-traumatic stress disorder*
SAD	*social anxiety disorder*

have been developed in attempts to further characterize animal and human conflict behavior and its relationship to psychopathology.[3,9-12]

Avoidance has been implicated as a cardinal symptom of anxiety disorders[13] and is thought to be an underlying mechanism maintaining anxiety. The majority of psychotherapies used to treat anxiety (eg, cognitive-behavioral and exposure-based therapies) aim to decrease such avoidance behavior.[14,15] Importantly, avoidance is an active choice process, ie, a *decision* that is made to sacrifice potential rewards in order to avoid potential negative outcomes. Individuals with strong avoidance drives in the absence of approach drives would most likely not experience distress and not present to the clinic—or would be given a diagnosis other than anxiety, such as Asperger's syndrome or schizoid personality disorder. Therefore, inherent in the notion of an anxiety disorder is conflict between approach-related drives (eg, to seek positive social interactions, to leave the house) and avoidance-related drives (eg, to prevent being humiliated or having a panic attack).

In this review, we propose that the approach-avoidance perspective provides an important framework for bridging the gap in knowledge about the relationship between brain and behavior, ie, to clarify the role of specific neural systems in anxiety. In particular, we review neural systems that, based on neuroimaging research related to approach, avoidance, and decision making, should be considered of utmost importance for approach-avoidance conflict processes. By combining knowledge regarding these neural systems with implications from current neuroimaging research in anxiety disorders, we will outline what important questions remain from an approach-avoidance perspective.

As this review focuses on a few brain regions likely to play a vital role in conflict decision making in anxiety disorders, we do not extensively cover every brain system potentially involved, nor do we discuss related neurotransmitter systems (eg, dopaminergic, serotonergic; for review see refs 2,16-19). Secondly, our discussion focuses on conflict *decision-making* paradigms and excludes paradigms in which prescribed behavior conflicts with automatic reactions (eg, inhibition or interference tasks[20,10]) and self-report measures of approach-avoidance or behavioral inhibition-activation.[21] Lastly, we will limit our discussion of anxiety disorders to generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder, specific phobia, and post-traumatic stress disorder (PTSD). We exclude obsessive-compulsive disorder because significant distinctions between obsessive-compulsive spectrum disorders and other anxiety disorders have been noted with respect to both symptom presentation and underlying neural substrates.[22]

Behavioral models of approach, avoidance, and decision making

Avoidance can be considered a drive motivated in response to stimuli and situations that threaten the integrity of the individual, ie, fear- or pain-inducing stimuli. Approach behavior can be considered a drive motivated by stimuli or situations that further ensure the integrity of the individual, ie, rewarding or pleasurable stimuli. Frequently, one has to make decisions among options that have both avoidance and approach features. We propose that understanding neural substrates of approach and avoidance processes and the arbitration of these values is necessary for understanding dysfunctions associated with anxiety disorders.

Neuroimaging studies of avoidance-related processing have relied heavily on passively experienced fear- or anxiety- producing stimuli, including pictures, sounds, smells, etc. However, a few studies have also investigated neural correlates of emotion regulation, fear conditioning, and fear extinction.[23,24] Approach-related processing can be investigated using passively experienced pleasurable or rewarding stimuli or appetitive conditioning.[16,25-27] Human neuroimaging research related to anxiety has thus far relied heavily upon passive fear or anxiety processing paradigms.

Several decision-making paradigms have been used to delineate the processes associated with arbitrating approach or avoidance-related outcomes. Specifically, risk-taking paradigms have been used in which the same option could be associated with winning or losing reward,[28,29] value-based decision-making tasks in which obtaining one reward requires sacrifice of another (eg,

paying money for food items[30]), and delayed-discounting tasks in which decisions are made between immediate and delayed rewards of various values.[31-33]

Although neural mechanisms of reward-processing and decision making have been a focus of some areas of psychopathology research (eg, substance abuse), there has been a lack of related research in anxiety disorders. Behavioral research provides initial evidence that reward-based decision making may be dysfunctional in anxiety. PTSD has been associated with decreased expectancy and satisfaction of rewards,[34] decreased willingness to exert effort to obtain rewards,[35] and decreased ability to learn optimal responses during reward-based tasks.[36] Research findings regarding decision-making processes in other anxiety disorders has not been as consistent. Individuals with high trait anxiety or specific phobia have reportedly exhibited impairment on the Iowa Gambling Task (IGT), a risk-based decision-making task(Aupperle RL et al, unpublished material).[37,38] GAD has been associated with intact performance on the IGT,[39] but increased errors during differential reward/punishment learning.[40] SAD has been associated with intact performance on reward/punishment learning,[40] but with exaggerated delayed discounting (greater preference for immediate over delayed rewards).[41] Panic disorder has been associated with intact IGT performance,[42] but with increased sensitivity to errors during a two-choice prediction task.[43] Obviously these findings are mixed, making it difficult to draw any firm conclusions regarding the extent or specificity of decision-making dysfunction across anxiety disorders. Further behavioral and neuromaging research is warranted in order to elucidate potential decision-making dysfunction that may contribute to approach-avoidance conflict difficulties and the underlying mechanisms of anxiety disorders.

Neuroanatomy of approach, avoidance, and decision making

Neural substrates underlying approach, avoidance, and decision making are integrated here with a particular focus on anxiety disorders. Neuroanatomical research in animals and human neuroimaging research on fear processing have implicated a cortico-limbic circuitry including the amygdala, insula, and prefrontal cortex (PFC)[44-46]—regions that have also been shown to exhibit dysfunction in anxiety disorders. Reward-processing and decision-making research has focused primarily on a corticostriatal circuitry involving ventral striatum/nucleus accumbens (NAcc) and frontal cortical regions—including the orbitofrontal cortex as well as more dorsal and lateral regions.[4,26,47-49] It should be recognized that regions outside of these corticolimbic and cortocostriatal loops are also implicated in these processes, including hypothalamus, thalamus, hippocampus, midbrain, parietal, and brain stem regions (for review of reward-processing and decision-making networks see refs 16,31,50; for review of fear-processing networks see refs 45,46,51). For this review, we will focus on a few regions that: (i) have been shown to play vital roles in determining the value of stimuli or choices during decision making; and (ii) we believe are likely to underlie approach-avoidance dysfunction in anxiety disorders. These regions include the amygdala, ventral striatum, insula, and PFC.

Amygdala

Avoidance and approach processing

The amygdala has been a primary focus of animal and human research related to fear processing, conditioning, and extinction.[52-54] Human neuroimaging studies implicate the amygdala in signaling fear- or anxiety-producing stimuli characteristics, including pictures, odors, and faces[55-57] as well as in signaling changes in reinforcing properties of stimuli, such as occurs during fear conditioning[58-60] or instructional and observational learning.[61,62] However, human neuroimaging studies have also shown the amygdala to respond to positive, rewarding stimuli and during appetitive conditioning,[16,26,27,63-68] suggesting this region may be involved in processing *salience* (eg, the emotional significance of stimuli), rather than simply negative valence per se.

Among the anxiety disorders literature, paradigms involving symptom provocation, anticipation of anxiety-provoking stimuli, fear conditioning/extinction, or processing of negative emotional faces, have been associated with exaggerated amygdala activation for GAD,[69-71] SAD,[72-78] panic,[79-81] specific phobia,[78,82-86] and PTSD[46,78,87-92] patients. Many studies report amygdala activation to correlate with anxiety symptom severity (SAD[75,94-96]; PTSD[87,88,96]) and suggest that amygdala activation decreases in response to cognitive behavioral or pharmacologic treatment (SAD[97]; phobia[98,99]; PTSD[100]). These results suggest that amygdala dysfunction in anxiety dis-

orders relates to aberrant signals concerning the presence of feared or negatively reinforcing stimuli—a dysfunction which can be at least partially rectified through treatment. However, it should be noted that some studies of GAD,[101] SAD,[102] phobia,[103-105] and PTSD[106-108] have failed to identify exaggerated amygala activation.

Although most neuroimaging studies of anxiety disorders do not explicitly aim to investigate responses to pleasurable or rewarding stimuli, many use such stimuli as "control" conditions and report neural activations during these conditions separately. These results are mixed, with some reporting no evidence of amygdala dysfunction (GAD[70,101]; SAD[93,94]; Phobia[109]; PTSD[88]) and others reporting exaggerated amygdala activation (SAD[73,110]; phobia[82]; PTSD[87]) to positive emotional stimuli or faces. This suggests that while amygdala dysfunction may be most evident for anxiety disorders during processing of highly salient, negative stimuli, such dysfunction may relate to emotionally salient stimuli in general. This could result in not only increased urges to avoid negative outcomes but also increased urges to obtain rewards—leading to a "higher-stakes" experience of having a lot to gain and a lot to lose, increasing the level of approach-avoidance conflict.

Decision making

Animal research suggests that the amygdala, and PFC-amygdala connections, play an important role in determining approach-avoidance behavior during conflict, delayed discounting (involving decisions between immediate smaller rewards and delayed larger rewards), and effort-based decision making (involving decisions between immediate easily attainable rewards vs larger rewards obtained after expending effort or energy)[111-113] (see reviews in refs 2,114). Similarly, patients with amygdala damage have been shown to exhibit impaired risk-related decision making,[115,116] and amygdala activation has been reported during decision-making paradigms involving uncertainty or risk.[117-119] A recent neuroimaging study implicated connectivity between amygdala/hippocampus and PFC (anterior cingulate [ACC] in particular) in the use of episodic imagery of future events to increase delayed discounting.[120] This suggests the amygdala may be involved in signaling risk and salience of future consequences.

The few studies that have examined neural substrates of decision making in anxiety disorders have, for the most part, not reported amygdala dysfunction. However, Krain et al[121] examined a group of adolescents with either GAD or SAD during a decision-making task involving various levels of certainty and reported that self-reported intolerance of uncertainty was related to greater amygdala activation during uncertain, or riskier, conditions.

In summary, although the amygdala has been a focus of the fear-processing and fear-learning literature in particular, this region seems to play a more general role in signaling salience of stimuli rather than simply negative valence.[122] The anxiety disorders literature provides evidence that the amygdala may be dysfunctional in signaling fear-related stimuli, but there is also initial evidence that this dysfunction may extend to salient stimuli in general.[46,78] Although the amygdala has not been the focus of neuroimaging research related to decision making, there is evidence to suggest the amygdala is involved in signaling uncertainty or risk of decisions.[117-117,121] We propose that the amygdala may have a primary role in signaling the presence, or potential future presence, of reinforcing stimuli as well as in gauging stimulus intensity. Such information is important in decision making and amygdala hyperactivation could relate to experiences of increased conflict or imbalances between approach and avoidance drives, such as observed in anxiety disorders.

Insula

Avoidance and approach processing

The insula is thought to play an important role in monitoring internal bodily states, predicting future internal states in response to environmental changes, and in seeking to maintain homeostasis.[123,124] The insula has been shown to activate in response to both pleasant and unpleasant somatosensory or emotional stimuli,[55,125-133] as well as during anticipation of future events.[140,141] The insula has been identified as important in the experience of drug craving and urges,[134,135] but also for learning the aversiveness-predicting properties of stimuli.[136-139]

Insula hyperactivation has been identified during symptom provocation, processing or anticipation of negative emotional stimuli, or in response to negative emotional faces in SAD,[78,142,143] phobia,[78,82,84,109,144] and PTSD.[46,78,90,145-147] Studies have reported insula activation to correlate with symptom severity (SAD,[94] PTSD[145]) and phobia treat-

ment has been shown to decrease insula activation.[98,99,148] However, there have also been several studies failing to identify insula hyperactivation in anxiety disorders (eg, SAD[74,93,95]; PTSD[106,108]).

The few studies reporting activations for positive emotional stimuli have, for the most part, either not reported on insula activation or have reported no insula dysfunction in anxiety disorders (GAD,[149] SAD[94]). Additionally, Straube et al[143] examined individuals with SAD and healthy controls and reported that while amygdala hyperactivation was observed for both happy and angry faces, insula activation was enhanced only for angry faces. This suggests that insula dysfunction may be circumscribed to negative valence in anxiety disorders.

Decision making

As mentioned, the insula is thought to signal potential changes in interoceptive state, and we propose that during conflict or decision making, the insula may be involved in predicting such changes to potential decisional outcomes. Animal and human studies of insula lesions have reported alterations in approach-avoidance behavior during effort-based and risk-related decision-making tasks.[150-153] Similarly, human neuroimaging studies and a recent meta-analysis implicate the anterior insula for paradigms involving risk and uncertainty.[29,154,155] An individual's predictions regarding interoceptive or emotional responses undoubtedly relate to his or her beliefs—developed through past experience or instructional/observational learning. There is some evidence that the insula plays a role in integrating information concerning current bodily state with cognitive information to make change predictions.[156] A recent neuromaging study utilized a paradigm similar to animal models of approach-avoidance conflict, which involved various levels of monetary reward associated with differing probabilities of shock. This study found that connectivity between insula and orbitofrontal cortex (OFC) was related to individual variability in decision making during trials involving both reward and punishment.[157] It is possible that insula-OFC connectivity is important for integrating individuals' preconceived beliefs about rewarding and punishing stimuli with information provided during the task to determine behavioral responses. In summary, the insula is thought to play an integral role in monitoring and predicting interoceptive state, particularly in response to affective stimuli.[124,158,159] Insula dysfunction has been identified in anxiety disorders—primarily during processing of negative emotional stimuli. The insula, particularly in its connections with the OFC, is proposed to also play a role in integrating beliefs with the current bodily state in order to make change predictions related to various choices.[156,157] This could be one way in which the brain estimates risk and influences decision making.[29] We propose that insula dysfunction in anxiety disorders could relate to imbalances in difference calculations regarding current and future interoceptive state, which could influence risk estimations and approach-avoidance decision making.

Striatum

Avoidance and approach processing

The epicenter of dopaminergic neurons, the ventral striatum (including the nucleus accumbens), has been identified as important for signaling rewarding or reinforcing properties of stimuli. This conclusion has been supported through animal research[16,160] as well as human neuroimaging research investigating responses to pleasant imagery,[161] auditory stimuli,[162] faces,[163,164] sexual arousal,[165,166] and food stimuli,[64,167] and during appetitive learning.[168-170] A meta-analysis reported that approximately 70% of studies involving provocation of pleasant emotion showed activation of the basal ganglia, including the striatum.[171]

Animal research suggests that, while some neurons within the ventral striatum respond to both rewarding and aversive stimuli,[172] NAcc neurons increase or decrease in activation to reward- and punishment-predicting stimuli, respectively[173] (for review see ref 16). Potentially related to this, human neuroimaging studies have reported striatal activation in response to aversive or unpleasant stimuli.[164,174-176]

Decision making

Animal research suggests that anatomical or pharmacologic manipulation of ventral striatal neurons influences approach-avoidance behavior during conflict,[177-179] delayed-discounting,[180,181] effort-based,[182,183] and risk-related decision-making models[184] (see review in ref 114). The directionality of lesion effects would suggest that this region is involved in orienting an organism towards reward. Potentially in concert with these findings, human neuroimaging studies report NAcc activation to corre-

late with the amount of risk involved in decisions[185,186] and to signal prediction errors between expected and actual reward value[187] (for review see refs 188,114).

The few neuroimaging studies investigating decision making in anxiety disorders provide initial evidence of striatal dysfunction. In PTSD, attenuated nucleus accumbens activation and difficulty learning the optimal response pattern during risk-related decision making has been reported.[36] Attenuated striatal activation in response to reward was also reported for PTSD during a wheel-of-fortune type task[189] and this striatal attenuation was related to level of "numbing" symptoms (eg, symptoms involving difficulty experiencing positive emotions or feeling distant from others). Although somewhat unrelated to decision making, an implicit memory task known to elicit striatal activation was used to identify striatal dysfunction in SAD[190]; while the same task failed to identify such dysfunction in phobia.[191]

In summary, this research provides evidence that the ventral striatum is involved in signaling the rewarding value of outcomes.[16,114,171,188] There is initial evidence of striatal dysfunction in PTSD and SAD,[36,189,190] as well as suggestions that striatal dysfunction may be related to PTSD-specific symptoms such as numbing. However, we propose it may also be important for approach valuations in other anxiety disorders and that an imbalance between striatal and amygdala/insula signals could relate to increased conflict and dysfunctional approach-avoidance behavior.

Prefrontal cortex

Researchers of different specialty fields use varying terminologies when referring to regions of the PFC. We will delineate the medial PFC as suggested by Amodio and Frith,[192] focusing on specializations of orbitomedial frontal cortex (OFC; including ventromedial PFC [vmPFC] and ventral anterior cingulate [ACC]) as distinguished from dorsomedial (dmPFC; dorsal ACC) and lateral (lateral OFC [lOFC], dorsalateral PFC [dlPFC]) regions.

Avoidance and approach processing

Medial prefrontal and particularly OFC regions are thought to play a role in regulating or inhibiting limbic regions and behavioral responses during fear processing. Neuroimaging studies in nonclinical populations report OFC and dorsomedial PFC (specifically dorsal and rostral ACC) activation in response to emotional pictures[55,133,171,193] and emotional faces[55,194,195] and provide evidence these regions are important for fear learning.[24,60,61,139,196,197] Animal and human studies provide some evidence of an inhibitory relationship between prefrontal regions (including OFC, dmPFC, and lateral PFC) and amygdala during fear extinction or emotional regulation.[198-202]

Human neuroimaging research supports implications from animal studies by showing the OFC to play a primary role in reward processing.[50,203] This region (as well as dmPFC) has been shown to activate in response to rewarding and reward-predicting stimuli, such as money, appetizing food, pleasant smells or music, attractive facial stimuli, and sexual arousal.[26,64,171,204,205]

PFC dysfunction has been repeatedly implicated across anxiety disorders, though the direction of dysfunction differs depending upon the paradigm and the anxiety disorder being examined. In response to symptom provocation or negative emotional stimuli, OFC and dmPFC (and occasionally lOFC and dlPFC) *hyperactivation* has been identified for GAD,[69,70,101] SAD,[72,74,206] phobia,[84,85,105,144,207] and panic.[79,208,209] Directional effects within the PFC have been mixed for PTSD,[47,78,89,96,210-214] though the majority of studies and meta-anlyses support *hypoactivation* of OFC and ventromedial regions.[78]

Experimental approaches involving instructed down-regulation of negative emotion have identified attenuated activity within OFC, dlPFC, and dmPFC regions in anxiety disorders (SAD,[201,215] PTSD[216]). These results have been taken as evidence that anxiety disorders are associated with decreased propensity to recruit PFC regions to regulate limbic activity and/or emotional responses. Additionally, SAD has been associated with an negative relationship between ventrolateral PFC and amygdala activation,[102] and PTSD has been associated with an negative relationship between mPFC and amygdala activation[96] during symptom provocation. Treatment of PTSD and phobia has been associated with increased dmPFC and/or OFC activations,[100,217-219] though other studies report phobia treatment to result in decreased prefrontal activation.[99,104,148]

Neuroimaging studies using positive emotional stimuli have, for the most part, either not reported or failed to find evidence of prefrontal dysfunction in GAD[70,101,149] and SAD.[72,220] However, Campbell et al[221] reported SAD to be associated with delayed dlPFC and dmPFC acti-

vation in response to happy faces compared with nonanxious controls. Additionally, panic disorder patients exhibited enhanced mid-ACC activation in response to happy faces[222]— the opposite of the attenuated ACC activation reported for fearful faces.[223]

Decision making

Decision-making research suggests the OFC is important for integrating information concerning the value of various stimuli or choice characteristics in order to bias the system towards one decision versus another. Animal research suggests the OFC plays a role in approach-avoidance conflict,[224-226] delayed discounting,[112,227,228] and risk-related decision making.[114,228,229] In human research, both OFC and dlPFC regions have been implicated in comparing values of various choices[188,230,231] and for ensuring successful decision making during the Iowa Gambling Task (dlPFC,[232,233] vmPFC[232,233]). Neuroimaging research has shown OFC to activate proportionally to the subjective value of stimuli during decision making,[31] and indicates it may be important for integrating sensory stimuli with cognitive information/beliefs to signal subjective value of stimuli.[234-237] Studies also suggest dlPFC-OFC connectivity may be involved in weighting various stimuli characteristics during decision making (eg, taste vs health characteristics of food[238]). The importance of the OFC in approach-avoidance conflict was also confirmed by Talmi et al,[157] who reported reward-prediction to be associated with OFC activation and individual variability during trials involving both reward and punishment to relate to insula-OFC connectivity.

Researchers have attempted to tease apart specific roles of various PFC subregions in processing decision-making characteristics, such as risk or delay calculations versus effort or action-based calculations. Animal research suggests that the OFC plays more of a role in the former, while dorsal PFC regions play more of a role in the latter.[16,31,114,239] This distinction, however, does not seem quite as clear in human neuroimaging research, as some studies support the OFC's role in calculating both the *value* of potential reward as well as the *effort* needed to obtain those rewards (eg, energy expense, receipt of shock[31,157,187]). Other studies support the dorsal PFC's role in risk-taking and delayed-discounting.[29,31,33,240,241] Human neuroimaging research has partially supported the distinctions between ventral and dorsal PFC by providing evidence that, while OFC regions are important for calculating *value* of choices, dmPFC regions are involved in selecting actions during decision making and detecting errors in those actions.[241]

The few studies investigating neural substrates of decision making in anxiety disorders have implicated mPFC dysfunction. PTSD has been associated with attenuated mPFC activation during risk-related decision making.[36] Self-reported intolerance of uncertainty in adolescents with GAD or SAD was associated with greater OFC (rostral/subgenual ACC) activation during uncertain, or risky, conditions of a decision-making task.[121] Additionally, SAD patients exhibited attenuated dmPFC activation during a "trust" decision-making game involving risk when contrasting conditions in which the other "player" was human versus a computer.[242] However, with this study, it is difficult to ascertain whether findings relate to risk processing or to the salience associated with supposed human interaction.

In summary, mPFC and OFC are considered important for processing both approach- and avoidance-related stimuli. These regions are thought to play an important role in negotiating and reconciling signals from other brain regions (eg, limbic, striatal, dlPFC) in order to calculate net values of stimuli and choices during decision making.[31] Medial PFC and OFC regions also play a role in regulating limbic and behavioral responses, particularly in the case of fear-provoking stimuli.[202] Anxiety disorders have exhibited OFC, dmPFC, and lateral PFC dysfunction during processing of negative emotional stimuli,[47,78] instructed emotion regulation (eg, refs 215,216), and decision-making processes.[36,121,242] We propose that OFC and mPFC dysfunction in anxiety disorders could be associated with difficulties in integrating signals from other brain regions concerning the various characteristics of a decision-making situation. Dysfunction of mPFC, striatal, and/or limbic regions could each have unique influences on approach-avoidance and conflict processes. Below, we present specific hypotheses to be tested by future anxiety research.

Summary: neural circuitry of avoidance, approach, and decision making

This review highlights the primary roles of amygdala, ventral striatum, insula, and prefrontal regions (OFC, dmPFC) in approach, avoidance, and decision-making processes (see *Figure 1* for pictoral representation of the proposed model). These neural substrates aid in computations of approach and avoidance valuations in decision-

making situations. The valuation itself is a dynamic process, and is related to current and predicted internal state. For example, if a stimulus predicts an outcome that challenges the integrity of the individual, eg, a drop in body temperature or shock applied to the skin, that option is evaluated as to be avoided. However, if the same option also results in reception of reward, the option has both avoidance and approach value. Thus, the individual needs to arbitrate between potential aversive and rewarding outcomes when faced with such a decision. We propose that approach-avoidance valuation may be dysfunctional for individuals with anxiety disorders. The precise type of approach-avoidance dysfunction awaits further experimental testing. Among the proposed hypotheses are: (i) over-representation of avoidance valuation; (ii) under- or over-representation of approach valuation; and (iii) insufficiency in integrating and arbitrating approach- and avoidance-related valuations.

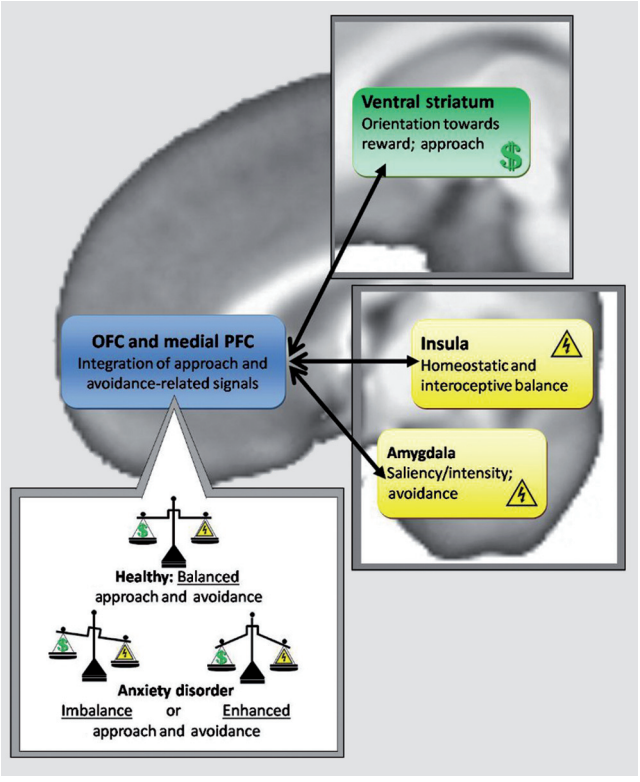

Figure 1. This figure summarizes the neural systems proposed to be integral for approach and avoidance processing as well as decision making, including the amygdala, insula, ventral striatum, and medial prefrontal (mPFC) and orbitofrontal cortex (OFC). Also represented are the proposed imbalance or enhancement of approach-avoidance signals that may underlie anxiety disorders.

Over-representation of avoidance valuations would presumably relate to dysfunction within amygdala and/or insular regions. Enhanced signals regarding salience of stimuli and expected emotional and interoceptive state changes could serve to overpower the system and orbitofrontal regions attempting to integrate these with other signals. This could, in essence, create a "signal-to-noise" problem[243] in which other important information is under-represented. We suspect that amygdala/insula dysfunction is likely to play a role in any observed conflict or decision-making dysfunction in anxiety disorders—as there is already plenty of evidence to implicate these regions in avoidance-related processing in anxiety.[79] However, one hypothesis to be tested is whether such limbic overactivation is the primary issue interrupting the dynamic approach-avoidance balance. If so, one may expect that aberrations in decision making would only be observed when the salience/magnitude of outcomes reaches a level in which there is significant recruitment of limbic regions or when the paradigm involves a component of risk for which the insula has been strongly implicated.[29]

Dysfunctional representation of approach valuation would most likely relate to ventral striatal dysfunction. Although only a few studies have reported striatal dysfunction in anxiety disorders,[36,189,190] there have also been very few studies attempting to examine neural dysfunction of anxiety during reward or decision-making processes. The hypothesis that striatal activation is involved in conflict decision making in anxiety populations is therefore one worthy of testing in its own right. If there is dysfunction in ventral striatal regions there remains the possibility of either attenuation or exaggeration of activation, and we propose that these two findings could relate to different symptom presentations or disorder subtypes. *Attenuated* activation could result in under-representation of approach valuation and relate to symptoms of numbness or depression often experienced as comorbid with some anxiety disorders.[244-246] At the experimental level, such striatal attenuation could result in decreased motivaton during effort-based decision-making tasks. *Enhanced* striatal activation could relate to over-representation of approach valuation. Concurrent enhanced representation of both approach and avoidance valuations could result in these signals "battling it out" against one another in order to influence the OFC and subsequent decision making. This in turn could relate to increased experiences of conflict and

anxiety within decision-making contexts. Such dysfunction could theoretically relate to intolerance of uncertainty, difficulty making decisions, and tendencies towards perfectionism, which are symptoms often associated with anxiety disorders.[247-249] At the experimental level, concurrently enhanced approach and avoidance valuation would theoretically result in increased reaction time and indecisiveness during decision-making paradigms—particularly those involving both reward and punishment, such as risk-based paradigms or approach-avoidance conflict.

Dysfunction in the integration and arbitration of approach and avoidance valuations would likely relate to OFC and/or mPFC dysfunction. The OFC is the prefrontal region most implicated in integrating information concerning various stimuli and outcome characteristics.[31] Rolls and Grabenhorst[49] have suggested that reinforcers must have "approximately equal potency at their maximal value to ensure that different rewards are chosen sometimes, and that behavior is not always directed towards a few superpotent specific rewards." We propose that the OFC may be responsible for scaling signals from various brain regions in order to enable comparisons to be made between them. By doing so, the OFC can then produce a signal that accurately reflects the net value of each potential outcome, biasing the system accordingly towards one behavior or another, and ensuring that responses represent a balance between approach- and avoidance-motivated signals. *Attenuated* OFC activation or a weakening in the correlation between OFC and limbic/striatal activation in anxiety disorders would suggest this is a primary site of approach-avoidance dysfunction, whereas *enhanced* OFC activation would most likely represent attempts to compensate for dysfunction in other regions within the proposed cortico-striatal-limbic system.

The hypotheses we set forth concerning OFC and mPFC, amygdala, insula, or striatal dysfunction in approach-avoidance processes in anxiety disorders can be examined on three different levels. First, specific behavioral experiments using decision-making paradigms can be used to disentangle effects of approach and avoidance from that of inefficient arbitration. For example, dysfunctions of approach-avoidance conflict may be examined during risk-related decision-making paradigms—particularly those modified to include affective-related outcomes (such as that used by Talmi et al[157]). Concurrent examination regarding the influence of effort and delay characteristics could be used to more fully delineate decision-making behavior. Second, functional neuroimaging can be used to determine whether the proposed segregation between approach and avoidance neural substrates and their relative dysfunction can be supported experimentally. In particular, neuroimaging research could utilize the framework of approach-avoidance conflict and decision making to more specifically delineate the role such dysfunction plays in determining the behavioral responses that are an integral part of anxiety disorders. Third, computational models developed within the decision-making literature[31,250] can be used to examine more formally the internal representation of approach and avoidance and its impact on computing behavioral alternatives. In closing, we recognize that much knowledge has been gained over the past 15 to 20 years of neuroimaging research concerning frontolimbic dysfunction underlying fear and anxiety processing in anxiety disorders. However, more needs to be done to integrate these findings with that of animal studies, and to link more directly with anxiety disorder symptoms, behaviors, and treatment effects. ❑

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Sistemas neurales en que se sustenta la aproximación y la evitación en los trastornos ansiosos

El conflicto aproximación-evitación es un importante concepto psicológico que se ha utilizado ampliamente para una mejor comprensión de la cognición y de la emoción. Esta revisión se focaliza en los sistemas neurales involucrados en la aproximación, la evitación y la toma de decisiones frente al conflicto y cómo estos sistemas se traslapan con los sustratos neurales implicados en los trastornos ansiosos. Se discute en especial el papel de la amígdala, la ínsula, el estriado ventral y las regiones prefrontales en relación con las conductas de aproximación y de evitación. Se proponen tres hipótesis específicas que subyacen a la disfunción en los trastornos ansiosos, las que incluyen: 1) la sobre-representación que se le da a la valoración de la evitación, la cual se relaciona con la sobre-activación límbica, 2) la sub o sobre-representación para la valoración de la aproximación, la cual se relaciona respectivamente con una activación estriatal reducida o exagerada y 3) la integración insuficiente y arbitraria de las valoraciones para la aproximación y la evitación, las cuales se relacionan con una activación reducida de la corteza órbito-frontal. Estas disfunciones se pueden estudiar experimentalmente utilizando versiones de paradigmas de toma de decisiones ya existentes, pero se pueden emplear también nuevas e innovadoras propuestas translacionales para investigar el conflicto aproximación-evitación y los sistemas neurales relacionados con éste en los trastornos ansiosos.

Systèmes neuraux impliqués dans l'approche et l'évitement dans les troubles anxieux

Le conflit de type approche-évitement est un concept psychologique important qui a été largement utilisé pour une meilleure compréhension de la cognition et des émotions. Cet article s'intéresse aux systèmes neuraux impliqués dans l'approche, l'évitement et le conflit décisionnel qui en résulte et au chevauchement de ces systèmes avec les substrats neuraux des troubles anxieux. Nous analysons en particulier le rôle de l'amygdale, de l'insula, du striatum ventral et des régions préfrontales par rapport aux comportements d'approche et d'évitement. Nous proposons trois hypothèses spécifiques sous-tendant le dysfonctionnement dans les troubles anxieux : 1) la sur-représentation de l'estimation de l'évitement liée à une suractivation limbique ; 2) la sous- ou la sur-représentation de l'estimation de l'approche liée à une activation striatale respectivement atténuée ou exagérée ; et 3) l'intégration et l'arbitrage insuffisants de l'estimation de l'approche et de l'évitement liés à une diminution de l'activation du cortex orbitofrontal. Ces dysfonctionnements peuvent être examinés de façon expérimentale en utilisant des versions de modèles existants de prise de décision, mais peuvent aussi nécessiter de nouvelles approches translationnelles et innovantes afin d'explorer le conflit approche-évitement et les systèmes neuraux qui y sont liés dans les troubles anxieux.

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