CHAPTER

2

Approach/Avoidance

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OUTLINE

1. BASICS OF APPROACH/AVOIDANCE—BEHAVIOR AND BRAIN

Approach and avoidance behaviors are fundamental to survival. As such, they depend on phylogenetically old systems with many conserved features. For this reason, the basic human brain systems for approach and avoidance have much in common with those of other species. Through study, we know more about the neurobiology of these systems and related traits than we do about most others, and this has translated into progress in human neuroimaging research. In this chapter, we lay out basic principles for understanding the processes of approach and avoidance, and then we briefly discuss neuroimaging research on the states related to them before discussing the progress in research on related personality traits.

Importantly, we define personality traits in terms of longer-term stabilities in patterns of states. That is, the level of a trait reflects the likelihood of being in a particular type of state, given a particular set of eliciting stimuli. The activation of approach and avoidance systems in any given situation requires careful long-term control of its precise intensity for any given input, and this long-term trait control of levels of activation is influenced by genes, developmental processes, and life events. These two systems and their associated traits can be seen as providing a foundation for the more complex processes from which mind and personality emerge.

Both the specific states that result from the activation of approach and avoidance systems and the longer-term sensitivities that tune these activations to match current functional requirements can be assessed indirectly through many techniques, including self-report and behavioral data. But increasingly the more direct measurements of neuroimaging are affording new insights. Detailed analysis of neuroimaging specific aspects of approach/avoidance systems is provided

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in chapters 3, 5 and 6 of the book. Here, we provide a more general overview of the fundamental nature of approach and avoidance, the systems that control them, details of a third system that resolves conflicts between goals, and the range of resultant states and traits that should be open to analysis by neuroimaging. It is important to note that within this chapter, we will use the simple term "avoidance" to refer to active avoidance (often termed withdrawal) and the terms "goal conflict processing" and "behavioral inhibition" to refer to passive avoidance. This is an important functional distinction, as these two forms of avoidance are mediated by different, and partially opposing, systems of behavior regulation.[1,2]

It is important to distinguish more general, positively motivated, goal-directed, behavior from object-specific consummatory behaviors (e.g., eating, drinking, and mating). Likewise, direct or very close contacts with specific affectively negative objects require specific defensive behaviors (e.g., attacking an enemy or avoiding contact with fluids from an Ebola corpse). There can be individual differences in these object-specific systems (with extreme sensitivity seen in clinical conditions such as uncontrollable aggression and stimulus-specific phobia). However, once there is even a moderate distance between the organism and the object, the adaptive requirements for approach or avoidance become essentially independent of the specific object—allowing us to talk about more general systems of approach and avoidance that are separate from specific consummatory and defensive reactions. Evolution, therefore, has shaped what can be seen as two general systems dedicated to approach and avoidance, respectively; reflecting the fundamental nature of these systems, they are represented in the major traits of personality.

1.1 Positive and Negative Goals

An important concept in dealing with mammalian approach and avoidance systems is the idea that they process goal representations. The nature of this internal representation needs some explanation and should be kept completely separate from the "goals" that people often attribute to behaviors in terms of external function (obtaining the food at the end of the runway) or evolutionary explanations (achieving survival).

The simplest approach behaviors can be controlled by the detection of gradients rather than by goal representations. A bacterium will approach food through the detection of, for example, chemical gradients in its immediate environment. It has receptors that can detect the strength of a signal (you can think of this as a smell or taste with chemicals) and move in the direction of increasing signal strength. Similarly, a simple multicelled organism can essentially scan gradients of physical stimuli by taking a twisting path through its environment or, when it is close to the source, by wagging its head or body. It then heads in the direction where the signal is strongest, which should ultimately lead it to its food even though it has no information as to the particular location at which it will ultimately arrive. Avoidance behavior can also be governed by gradients. For many organisms, being in the light is dangerous. So even simple detection of light strength allows the organism to move in the opposite direction and find safety (Figure 1).

These kinds of movement, controlled by a local gradient, are called "taxes"[3] (pronounced *tack-seize*). Taxes are often taken to involve a reaction to only very simple stimulus aspects—so that light intensity (as in Figure 1) would be included but visual stimuli that depend on form would not.[3,4] Critically, taxes are not goal-directed in the sense that the series of individual behavioral steps are not determined by a single internal representation of their endpoint. Although each behavioral step can be viewed with the goal of reducing the current light level, the final point at which the animal comes to a halt is simply the point at which such a sequence self-terminates and is not represented internally. That is, the maggot follows a path determined by the local gradients even if that is a circuitous route and does not terminate in the darkest place in the environment, whereas a rat controlled by a goal-representation will often take a straight-line path through a strongly lit area to reach the darkest area. So, as external observers, we can often see taxes as causing an organism to reach a "goal" (in a functional and/or evolutionary sense), but the behavior of the organism itself is not driven by an internal representation of the end state of the sequence of behaviors.

So, what is a goal for an organism? What kind of internal representation is a goal? Imagine you are a hungry rat and you have just been placed in a T maze by an experimenter. If you are hungry and you know from previous experience that there is food and it is at the end of one arm, then that particular food-bearing arm will be a goal for you. The other arm does not have food and so is not a goal for you at the moment. Likewise, if the food is moved to the other arm (and you know that it has been moved), that arm will now become your goal. However, if you are not hungry, even the arm with food will not be a goal, and you will probably decide to curl up in the end of the start arm and have a snooze (experimenters often test rats in the day time, which is the time they normally sleep). A goal, therefore, has both cognitive/identifying and motivational/consummatory properties. Its cognitive properties distinguish it from other places, times, or combinations of stimuli that may have the same motivational properties (we will refer to each specific set of such cognitive properties as a "situation"). Its motivational properties derive from the organism's current need to acquire some specific stimulus—food, drink, etc.—and

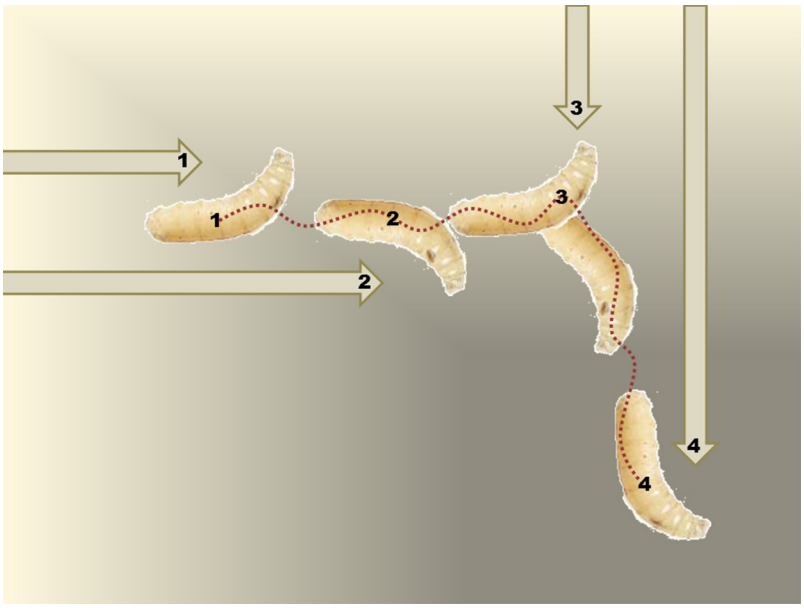

FIGURE 1 After feeding, maggots head for the dark. If light comes from the left, it is detected by head receptors when the maggot turns its body up (point 1), making it turn away (point 2). Successive turns away from the light take the maggot to the right (dotted track). At point 3, the light instead comes from the top. Turns away from the light now move the maggot downwards. *Based on Figure 7.3 in Hinde.*[4]

the presence of the relevant motivational stimulus in the situation. Importantly, neither the "situation" nor the "motivation" by themselves will generate goal-directed behavior. It is their compound "goal representation" that does so. In contrast, while we can discern "goals" for behavior in an evolutionary sense (e.g., the goal of random exploration could be said to be the discovery of food), this behavior is not goal-directed in the sense that behavior is controlled by an internal representation of the end point of the behavioral sequence.

To say that an animal has a goal needs some justification. How do we know that a rat's behavior is not simply the result of taxes or, in the case of complex, learned running in a maze, simply a long sequence of stimulus-response reactions that act like a string of taxes? In an experiment where a tone predicted a shock, it was found that a sheep lifted its leg off the pad that delivered the shock. Had the sheep learned a simple stimulus–response relationship? If the sheep was turned over so its head was on the pad, it lifted its head rather than its leg in response to the tone. Even in this very simple case, the sheep has clearly learned the relationship between the two stimuli and has not learned a fixed "conditioned response."[5] Or, suppose you inject a rat with enough anesthetic to seriously affect its coordination; it will still immediately escape from a box where it has been shocked using new movements that can include rolling out of the box.[6] Or, if you lesion its motor control systems, it can navigate a complex maze perfectly accurately using quite new movements. "The essential point here is that the new movements are not stereotyped, but selected from variable patterns in such a manner as to bring the animal nearer the goal. Furthermore, the new patterns are directly and efficiently substituted without any random activity."[4] In all these cases, the animals are demonstrating control of behavior by an internal representation that is a compound of an identifying situation and a motivating consummatory stimulus, which calls forth whatever behaviors are available to the animal, given the situation, to achieve consummation.

We also need to be clear that, in this sense of situation–motivation compound, there can be two very different types of goals relating to approach or avoidance, which can conflict with, or reinforce, each other in the control of behavior. The word "goal" is typically used in English to signify something we want to achieve in the positive sense. As we have already seen, there can be positive and negative taxes (with the organism moving to increase or decrease the relevant signal, moving up or down its gradient, respectively). Likewise, there can be positive and negative goals, with the goal creating what might be called a "cognitive gradient" that then determines the animal's specific behavior. A positive goal is an attractor, something to be included in the desired future state; a negative goal is a repulsor, something to be excluded or avoided in the desired future state.

In the top left-hand panel of Figure 2, a shock or some other unpleasant event or object is represented in the bottom left-hand corner. If a rat is aware of this danger, it will run directly away—shown by the arrows in the figure—and the tendency to run will decrease as the rat moves away from the object.[7] The object is a repulsor. The red zone represents all the paths that will be taken by any rat, and its grading represents the change in

running strength, resulting from the cognitive gradient created by the rat's internal representation of the danger. Conversely, in the top right-hand panel is the equivalent representation of the paths taken by a rat running to food, or some other attractor, that is in the top right hand corner of the rectangular box. The only substantive difference between the shock and the food is that the direction of movement, relative to the gradient, is the opposite—as with positive and negative taxes.

Whether behavior is controlled by a positive or negative goal can be difficult to determine without careful analysis. It might seem obvious that danger is negative. However, when faced with danger (such as a cat), a rat may be motivated to seek safety (its home burrow), which constitutes a positive goal. In many threatening situations then, both avoidance of danger and approach to safety can occur. Typically, when close to danger, the rat will avoid it (moving directly away from the danger because any other path will take it closer to the cat and increase the chance of being caught), and when close to its burrow, it will head straight for that. The result (Figure 2, bottom panel) will be a curvilinear path in the simplest cases with the initial running being avoidance of the negative goal of danger and the later running being approach to the positive goal of safety. With several examples of the same situation and with an animal starting in different positions, we can determine the nature of the controlling goal from the set of trajectories. If they diverge from a point (as in Figure 2, top left), then they are controlled by a negative goal and if they converge (top right), then they are controlled by a positive goal.

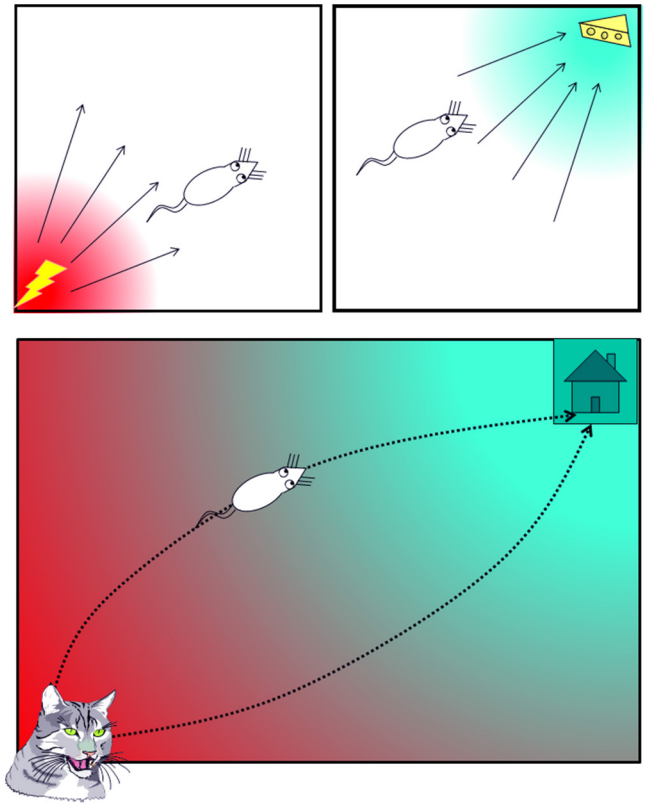

FIGURE 2 Diagrammatic representation of cognitive gradients created by shock (top left), by food (top right), and by the combination of danger and safety (bottom). The solid arrows represent the direction of movement of a rat located at the base of the arrow. The dashed curves represent the path taken by a rat from danger to safety (see text).

1.2 Valuation versus Motivation

The positive or negative nature of a goal is not determined just by whether the stimulus generating the situation is itself positive or negative. In the example that we just considered of the rat fleeing the cat, the presence of the cat generates a negative goal at one point in space, but the absence of the cat (guaranteed by the nature of the burrow) generates a positive goal in the burrow entrance. (If there is no burrow, then the rat will simply run directly away from the negative goal—as in the top left panel of Figure 2—until it reaches the limits of the apparatus since there is no safe place to attract it.)

The capacity of a single class of motivational stimuli to give rise to opposite goals in different circumstances is most obvious with consummatory stimuli (like food and water) and in economic experiments. The presentation of a positive stimulus produces positive goals, but the omission of expected food, omission of expected water, loss of money, and any other negative contingencies of positive events generate the aversive state of frustration.[8–10] The situation linked to omission or loss will therefore be associated with negative motivation, and so their compound will be a negative goal. When the same situation occurs in the future, it will then generate avoidance, thereby reducing exposure to frustration. An important point here is that the immediate experience of frustration produces escape,[11] fighting,[8] learned avoidance, and many other responses that are also typical of the immediate experience of pain.[12] In general, the omission of negative and positive events can be treated as having the same effects as the presentation of positive and negative events, respectively.

The idea that omission of a positive event creates a negative goal in exactly the same way as presentation of a negative event requires one caveat—the two outcomes do not have the same value. For an event to affect behavior, it must first be valued. This value, for any given object, will vary with both time and the particular individual. Gorgonzola cheese will have a high positive value for many hungry adults but will usually have a high negative value for young children. Likewise, a rat that is not hungry will not value food highly (i.e., will not work hard to obtain it), and a rat that has undergone taste aversion conditioning for a particular flavor will not value a food with that flavor but will value other food. You might think that a specific object (like a dollar)

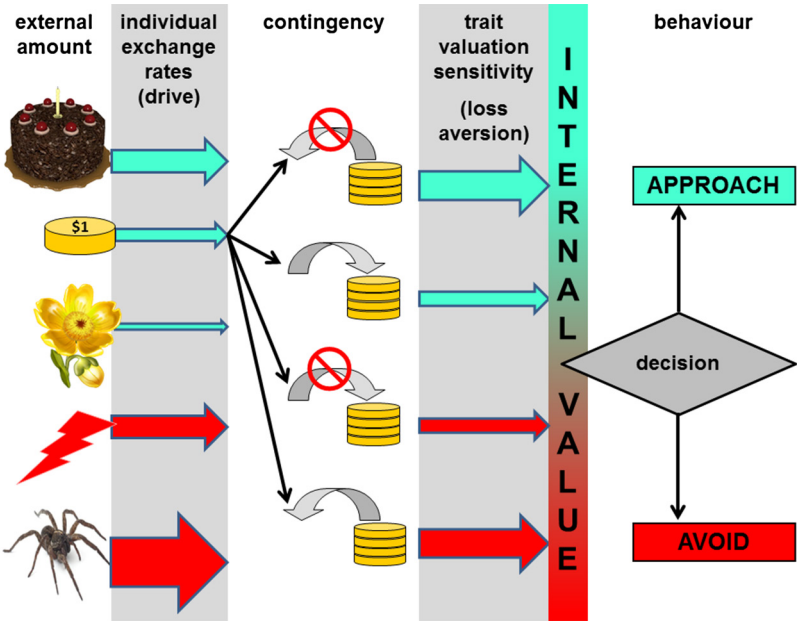

FIGURE 3 Relations between external amount, contingency, and value. An external item will have a specific amount (e.g., one entire cake) that, together with the current level of drive (which acts like a currency exchange rate) for that kind of item for that person, determines its primary internal value (thickness of arrows in first column). As shown for the case of $1, this interacts with whether the item will be gained or lost to determine the direction and size of its internal value as ultimately measured by the effect on behavior. The direction of this effect is reversed if the gain or loss is omitted. Loss (removal from a store of items) is most easily controlled with money but will also occur when, for example, one rat steals the food from another rat.

will have the same value, whether it is being gained or lost—after all, it is the most fungible of all stimuli. But it turns out that, in a wide range of situations, a lost dollar is treated as having greater value than a gained dollar. That is, someone will work harder to avoid a dollar loss than they will to make a dollar gain. This important and very general phenomenon, discovered in behavioral economics,[13–15] is termed loss aversion.

Individual differences in valuation are often not important for scores obtained in experiments in which some manipulation affects approach or avoidance. For example, individual variation in hunger drive among a group of rats will simply increase variation in the running speed within a group and will not, in the absence of sampling biases, change the difference between the means of the groups. However, there are times when we may want a full understanding of the effects of individual variations in approach and avoidance tendencies. There are often times, in particular, when we want to assess the long-term sensitivities of approach and avoidance systems (i.e., individual personality traits). If so, we will want to take account of both the valuation of specific objects (via their specific exchange rates in relation to the single internal currency on which choices are based) and whether the situation involves a positive or negative contingency with the occurrence of the object (Figure 3). If we use only positive objects to assess trait approach, our measures will be confounded by the variation in trait positive valuation. It should also be noted that valuation, as we have used it here, involves an essential interaction between "wanting" and "liking" components of a positively valued object that have different neural correlates.[16,17]

1.3 Goal Interactions, Gradients, and Goal Conflict

Approach and avoidance behavior are fairly simple to understand when there is only one goal. However, when more than one goal is available, we need to consider the way goal gradients interact and the special effects that occur when goals are in conflict with each other.

We have already seen one simple example of interaction between two goals. The rat first fleeing from the cat and then racing toward safety (Figure 2) has two compatible goals. Which goal is in control depends on the rat's position and the fact that the effect of a goal has a gradient (i.e., a decrease in the strength of the effect of the goal on behavior as distance increases). These gradients are represented by the fading of the colors with distance from the points at which each goal is located. In one sense, it is obvious that a rat should first run directly away from a cat, as this means it is least likely to get caught. However, more mechanistically, we can say that, at a very short distance, the effect of the cat is strong and so produces avoidance, while the effect of very distant safety is weak and so produces minimal approach. The reverse is true at the other end of the rat's trajectory: at

intermediate distances, we see a balance of push and pull in operation, with both tendencies generating much the same running movements.

The notion of the diminution of the strength of a goal with distance is intuitively obvious. But it has also been demonstrated in a range of experiments[18] that test, for example, how strongly a rat fitted with a harness will pull to move toward a positive goal or away from a negative one.[19] A similar diminution is seen with delays between action and the achievement of a goal—a phenomenon referred to in behavioral economics as "temporal discounting," which shows a gain/loss asymmetry[20] similar to that shown with simple value.

A more problematic interaction, from the point of view of both the organism and the experimenter, is the interaction between incompatible goals. The theoretically simplest example is what is called approach-avoidance conflict. For example, if a hungry rat is placed in one end of a straight alley and knows there is food in the goal box at the other end, it will run to this positive goal. However, if we also arrange it so that it will receive a shock in the goal box, the resultant behavior is not simple. With a weak shock, it will run slower but still reach the goal box. With a moderate shock, however, it will start to run, slow down as it gets closer to the goal box, and then dither to-and-fro. None of this can be explained by a simple economic calculation that subtracts the intrinsic value of the shock from that of the food, which would result in the rat either not running at all (receiving neither food nor shock) or always running all the way to the goal box (receiving shock but also food).

To understand approach-avoidance conflict, we need to look at the nature and interaction of the positive and negative goal gradients affecting the rat. The experiments with rats in harnesses[19] demonstrated that the fall-off with distance of the power of a goal is much greater for a negative one than a positive one. These gradients and their summative interaction[7,21,22] are shown in Figure 4. Initially, because its gradient is shallow, the positive goal (the memory of food) attracts the rat. In the absence of shock, the rat would run progressively faster as it got nearer to the goal box. But, part way down the runway, the negative goal (the memory of shock) begins to affect the rat, slowing it down and making its path less direct. If the shock is strong enough, so that the negative goal is more highly valued than the positive goal when the rat is in the goal box, then at a point before the goal box is reached, the approach tendency and the avoidance tendency will be equal, and the rat will not reach the goal box.

Approach-avoidance conflict does not simply make the rat stop running. The positive and negative values do not just cancel out, leaving the rat unmotivated. Instead, at the balance point, the rat will dither between approach and avoidance, turning first away and then back toward the goal box (dashed path in Figure 4).

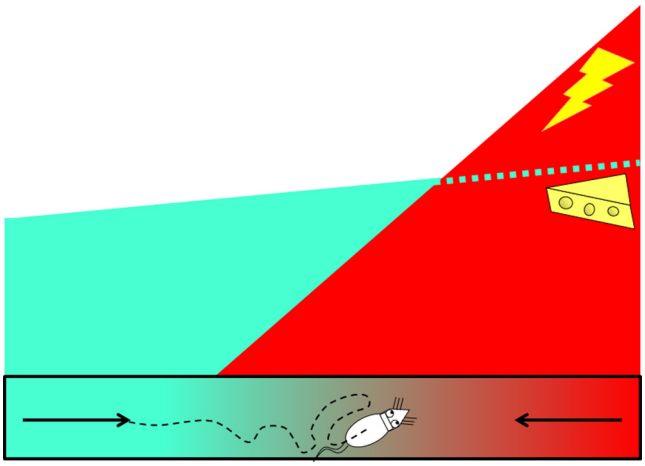

FIGURE 4 Interaction of approach and avoidance gradients. Positive goals (e.g., cheese for a hungry rat) have an effect on behavior that decreases slowly with distance (green). Negative ones (e.g., shock) have a steeper gradient (red). Their interaction (graded color in bottom panel) means a rat will initially run toward food but then will stop part way if there is a shock (see text).

(We also dither, experiencing strong emotion, as we wonder "should I stay or should I go," etc.) Approach-avoidance conflict will also often produce what appears to be completely irrelevant behavior, such as grooming. This is technically termed "displacement activity,"[3] and you are likely to have experienced this in yourself: chewing your nails as you worry about what to do or pacing up and down as you wait for a challenging interview.

The novel behavioral patterns elicited by approach-avoidance conflict and the effects of antianxiety drugs on them, but not in simple avoidance,[23] show that a third system, beyond the approach and avoidance systems, is involved. Termed the "Behavioral Inhibition System" (BIS), and described in considerable detail by Gray,[1,18,24] this system has outputs that inhibit the behavior that would be generated by the positive and negative goals (without reducing the activation of the goals themselves), increases arousal and attention (generating exploration and displacement activities), and increases the strength of avoidance tendencies (i.e., increases fear and risk aversion). Increased avoidance during goal conflict is adaptive since, faced with risk, failing to obtain food or some other positive goal is likely to be easy to make up at another time, but experiencing danger could have severe consequences. This increase in aversion produced by goal conflict is sensitive to anxiolytic drugs. So, if the rat shown in Figure 4 is treated with an anxiolytic drug, it will no longer dither and will approach closer to, and sometimes reach, the goal box[25,26]—since the drug affects the passive avoidance generated by goal conflict but not basic approach or basic active avoidance tendencies.[23]

As with approach and active avoidance, the functional requirements of approach-avoidance conflict are sufficiently fundamental that passive avoidance appears

early in phylogenetic terms, being present in coelenterates[27] with anxiolytic benzodiazepine receptors appearing in primitive vertebrates, such as the lungfish, and being present in fish, amphibians, reptiles, birds, and mammals.[28]

1.4 Hierarchical Control

An important feature of neural systems is that they are hierarchically organized. Both in terms of evolution and development, neural systems must fulfill preexisting adaptive requirements while adding the machinery for more sophisticated functions. As a result, higher order circuits are overlaid on lower order ones, and whether behavior is controlled by a quick and dirty, or slow and sophisticated, circuit can depend on time pressure.[29] For example (Figure 5), incoming information can be evaluated quickly, but only sparsely, in the thalamus. If an important stimulus (e.g., a potential danger) is detected, a signal can be sent directly (and so immediately) to the amygdala, which can start taking action. The incoming information is then passed to the cortex for more detailed (and so slower) processing. If the cortex confirms the thalamic evaluation, action (e.g., avoidance) is continued; if it disconfirms, then different action can be initiated. Critically, in the bulk of situations, raising a false alarm has few consequences, while a slow response to a real threat can be fatal; this is a variant of the "Life-Dinner Principle," namely that it is better to sacrifice one's dinner than one's life.[30]

With the generation of either approach or avoidance behavior, the control of simple motor acts and of larger scale actions is essentially independent of the type of goal. Running through a doorway involves the same basic perceptual-motor requirements whether you are attempting to leave one room because there is a snake in it or enter the next room to get the last cookie before your friends reach it. There is, therefore, a simple hierarchical organization of control systems, from act to action to goal[31–33] (Figure 6), which means that neuroimaging can focus on particular levels of the system when asking specific levels of questions.

The most immediate control is of what we will call "acts." These are selected in more posterior parts of frontal cortex close to the primary motor strip–supplementary motor area/SMA and Area 8 (including frontal eye control fields). (For details of the numbered cytoarchitectonic cortical areas defined by Brodmann, see the Figures provided in most neuropsychology text books, e.g., Kolb & Wishaw[34] Figures 1–10, Bear, Connors and Paradiso[35] Figure 7.26.) Sets of acts make up "actions," which require deeper levels of processing (i.e., requiring more computational layers or more recursive cycles between a fixed set of layers). These are selected in parts of dorsolateral and lateral orbitofrontal

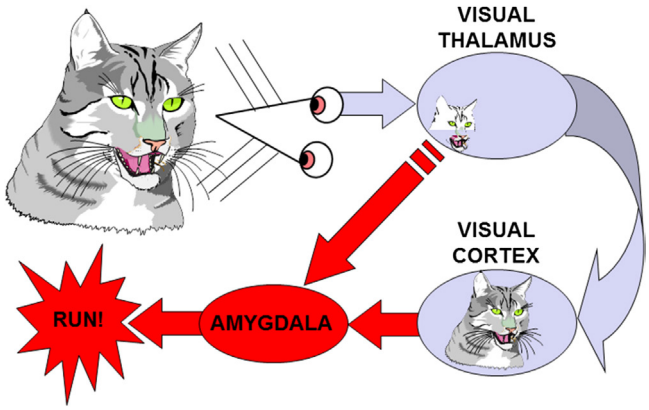

FIGURE 5 Quick and dirty perceptual processing in parallel with slow and sophisticated. Initial partial processing by the thalamus produces a quick, potentially wrong, response. Slower processing through the visual cortex will be more accurate but not desirable if survival depends on speed. *Based on Ledoux.*[29]

cortex (OFC)—among the many other functions of OFC. Sets of actions, in turn, are shaped by goals, which not only require even deeper processing but also include a motivational component, distinguishing between positive and negative valence. Goals are selected by limbic areas (anterior cingulate/ACC, prelimbic, infralimbic, and medial OFC). These act/action/goal control systems can be viewed as hierarchically organized, not only because of the progressive ordering of their functions, but also because they are interconnected and progress from the most recent isocortex through to the oldest allocortex and because they all have the same fundamental pattern of connections with subcortical structures (Figure 6). Analysis of approach/avoidance (as opposed to generic motor control independent of the goal) is therefore analysis of the way activity in limbic systems controls other aspects of the brain.

A final important aspect of hierarchical control—the matching of psychological to neural hierarchy—has been most studied in relation to avoidance and behavioral inhibition. Careful analysis of the behaviors of rats faced with cats in the laboratory determined that specific avoidance-related behaviors occurred when there were different distances between the rat and the cat.[37–40] Defensive distance reflects both a negative goal gradient of the type we have already discussed and a hierarchy of behavioral responses ranging from quick and dirty to slow and sophisticated. Importantly for neuroimaging, this behavioral hierarchy maps to a similar hierarchy of neural structures ranging from caudal (and phylogenetically old) to rostral (and phylogenetically recent).[41,42] We have suggested[2] that the systems controlling avoidance and behavioral inhibition can be seen as having a parallel hierarchical organization of this type (Figure 7(A)), where the position on the gradient of defensive distance determines the neural level that will be maximally

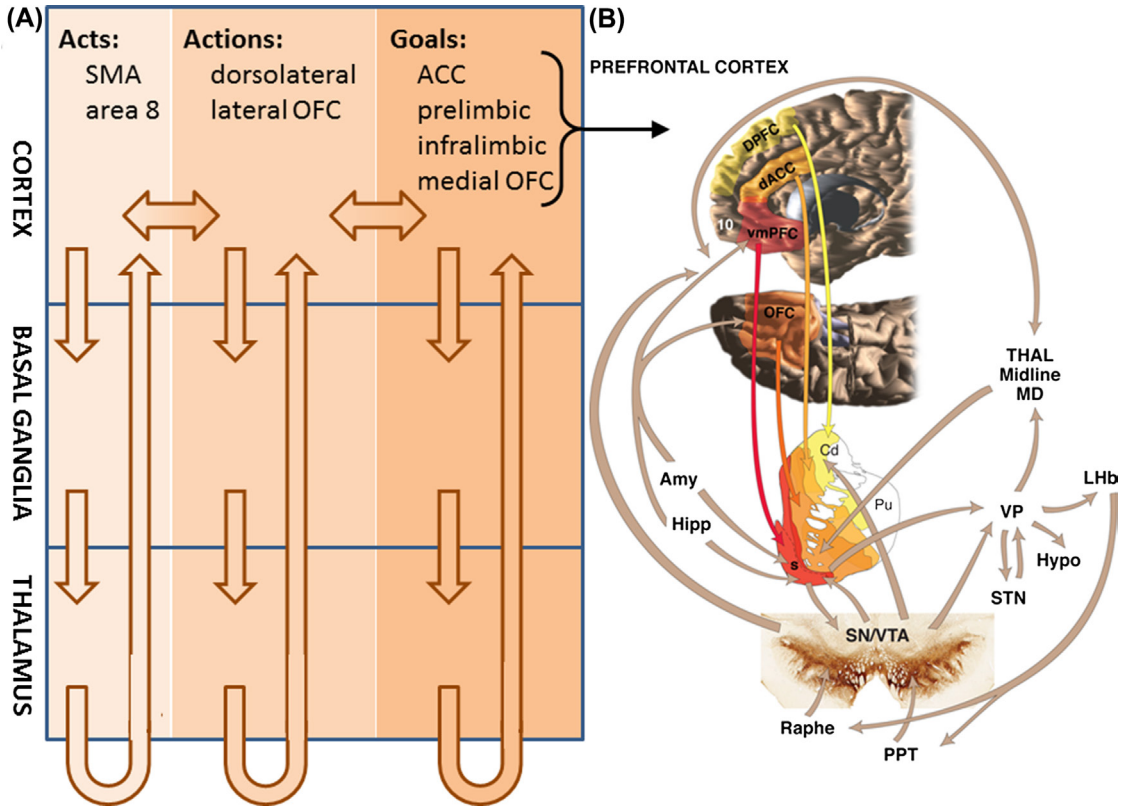

FIGURE 6 (A) Acts, actions, and goals are processed by different, interacting levels of the frontal cortex. These can be seen as parallel systems and have similar topographic relationships with the same subcortical areas.[31–33] Abbreviations: ACC = anterior cingulate cortex; OFC = orbital frontal cortex; SMA = supplementary motor area. (B) A more detailed picture of goal processing areas that process reward-related information, showing the retention of topographic organization (yellow-red arrows) of the direct connections of the various cortical areas to the basal ganglia, specifically the ventral striatum. They are also less directly connected via a range of other areas (brown arrows). *Reprinted by permission from Macmillan Publishers Ltd: Neuropsychopharmacology,[36] copyright (2009).*

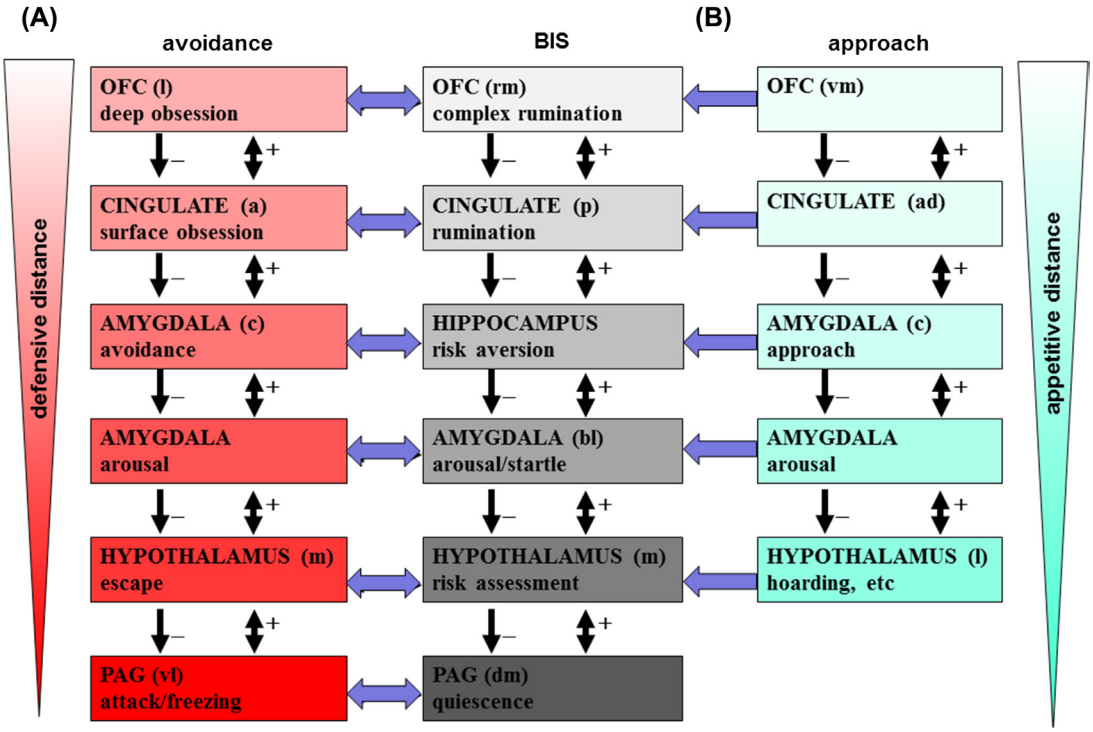

FIGURE 7 (A) Hierarchical organization of avoidance and behavioral inhibition (BIS) in terms of behavior and neural level. Lower levels process small defensive distances; higher levels process greater ones (i.e., negative events that are more distant in space or time). Activation tends to spread through the whole system (double-headed black arrows) but strong activation of a higher level (e.g., avoidance) inhibits (single-headed arrows) the behavioral output from (but not the activation of) lower levels (e.g., escape). *(Adapted from McNaughton and Corr.[2])* (B) Postulated equivalent organization of approach.[36,43,44] Abbreviations: PAG = periaqueductal gray; OFC = orbital frontal cortex.

activated and in control of behavior, and the presence of a sufficiently strong conflicting approach tendency will switch control from the avoidance system to the BIS. Although this has been less explicitly elaborated, it appears that the approach system (often referred to as the behavioral approach system, or BAS) has a similar hierarchical organization[16,36] (Figure 7(B)).

As with the motor control system, appropriate inputs activate multiple modules (anatomically localized processing units) within these systems both via direct input and via reciprocal connections between the modules. The selection of a particular module for the control of behavior essentially involves a release from inhibition (allowing control to pass quickly between modules that are already primed to produce output). Where a higher level module controlling more sophisticated responses (e.g., simple active avoidance) is highly activated, it will inhibit the specific behavioral outputs from lower level modules controlling quicker and dirtier responses (e.g., undirected escape). However, to permit fast switching between such behaviors and because the behaviors share common autonomic requirements, activation of the higher order module will not reduce (and can increase) the activation of lower order modules. As a result, although behavioral output from the lower order modules is blocked, other outputs to the sympathetic nervous system will still occur.

1.5 From System Architecture to Neuroimaging

On the face of it, the neuroimaging of approach and avoidance behaviors could not be simpler: we would first develop a task that motivated simple approach and simple avoidance, and then we would observe blood-oxygen-level dependent (BOLD) or electroencephalogram (EEG) signals during the performance of these behaviors. We would create a contrast with an appropriate control condition to ensure that we were measuring motivation-specific processes. However, our description of the complexities of the generation of approach and avoidance behavior should warn us against this seductively simple approach.

Specifically, it can be seen from our overview so far that the neuroimaging of approach/avoidance states and traits needs to take primary account of three basic systems: controlling approach, avoidance, and goal (e.g., approach-avoidance) conflict (the BIS). Neuroimaging that is intended to be specific to approach, avoidance, or conflict also needs to take into account the valuation of affective stimuli, which will differ for a gain and a loss of the stimulus as well as being transient (e.g., the value of food will depend on the current level of hunger). Simple actions (like running) can fulfill both approach and avoidance goals, and so a substantial part of the frontal cortex, basal ganglia, and thalamus can be ignored (Figure 6) if we are interested in *differences* between approach and avoidance systems, which we expect to involve limbic goal control areas. (That said, the strength of activation of the approach, avoidance, and goal conflict systems could be assessed via variation in their output to act and action systems in the same way as it can be assessed by the strength of behavioral output, e.g., speed of running.)

At the state level, for each of approach and avoidance, we should expect activation of specific modules of distinct hierarchically organized systems spanning the caudal subcortex through to the rostral cortex. The specific module (and system) momentarily controlling behavior will vary with the location of the animal within the current goal gradient(s), as well as with variations in the external amount of the motivating stimulus and with the internal valuation of that amount. However, because of the common inputs from objects in the world to different modules and because of reciprocal interconnections between the modules (Figure 7), many modules of these systems will be active simultaneously and so, to an approximation, we can also expect to detect some activation of the system as a whole.

This holistic view of approach and avoidance systems is even more appropriate at the trait level. Not only, as we have noted, are the systems strongly interconnected, but there are both evolutionary and pharmacological reasons for expecting trait modulation to often act on each system as a whole rather than targeting one specific module. This has important implications when we consider the neuroimaging of basic systems of personality.

First, in adaptive terms, we would expect sensitivity to motivationally significant stimuli to impact on the systems as a whole. In many cases, for example, an increase in the intensity of a threat is equivalent to (if not caused by) a decrease in defensive distance. Thus any trait adjustment (genetically or through development or learning) of the general strength of approach or avoidance responses will act primarily to determine which module of a system is activated at any point in time rather than altering only the intensity of activation of a single module. More module-specific trait sensitivities would affect the probability of a particular class of output. For example, there could be a selective increase in the probability of panic or of obsession to any given level of threat input without a change in more general threat sensitivity (fearfulness).

Second, pharmacologically, the systems can be viewed as relatively homogenous. This is clearest in relation to the role of serotonin, noradrenaline, and endogenous benzodiazepine ligands in avoidance and behavioral inhibition but is likely to be similar in relation to the role of dopamine and endogenous opiates in approach. As shown in Figure 8, the relatively small

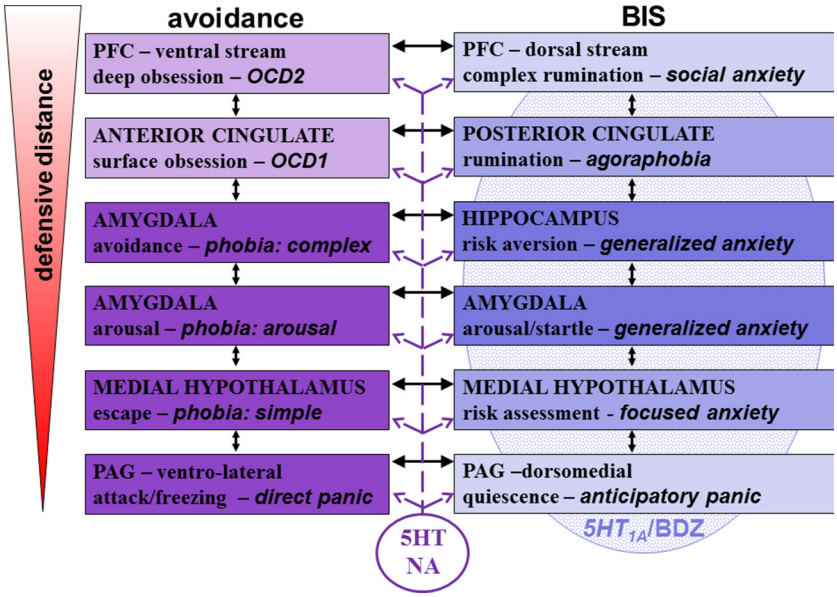

FIGURE 8 Pharmacology of avoidance and behavioral inhibition (BIS). Anxiolytic drugs—$5HT_{1A}$ agonists, BDZ—act (blue shading) on structures of the BIS to reduce the effects of goal conflict but do not affect active avoidance behaviors. More complex forms of anxiety tend to be less affected (lighter shading). Panicolytic drugs—via 5HT and NA transporter and breakdown systems—act (purple shading) on structures of the avoidance system to reduce panic and avoidance and also on structures of the BIS (where increased 5HT leads to increased $5HT_{1A}$ activation) to reduce goal conflict. Because of variations in the 5HT transporter systems, only some panicolytic drugs also reduce obsessions (lighter shading). Abbreviations: 5HT = serotonin; $5HT_{1A}$ = serotonin 1A receptor; BDZ = benzodiazepine; NA = noradrenaline; OCD = obsessive compulsive disorder; PAG = periaqueductal gray; PFC = prefrontal cortex. *Adapted from McNaughton.*[2,45,46]

numbers of serotonin and noradrenaline cells in the raphe and locus coeruleus send multiple collaterals that innervate essentially the whole of the systems controlling avoidance and behavioral inhibition. Genetic, developmental, or situation-related variation in synthesis and release would tend to affect the two systems as a whole—essentially altering defensive distance for both avoidance and behavioral inhibition. Similarly, although there appears to be some variation (see blue shading in Figure 8) in the density or effectiveness of benzodiazepine receptors among brain areas, endogenous benzodiazepines can essentially impact the whole of the BIS, altering goal conflict sensitivity independent of defensive distance. Likewise, relatively small numbers of dopamine neurons send collateral innervation to vast areas of the frontal cortex and basal ganglia and so are able to modulate approach systems quite generally. (Note, however, that the dopamine system does not merely control approach behavior; rather, it more generally facilitates flexibility in behavior to learn from and take advantage of possibilities that arise from failures of prediction.)[47]

Module-specific traits could result from more local changes in the same systems. For example, pharmaceutical companies have created compounds that target obsession more than panic, and vice versa. They take advantage of differences in the transporter molecules existing in different neural areas to produce area-specific alterations in the level of transmitters in the synaptic cleft for any given released amount. Genetic variation in transmitter uptake among these areas could, therefore, give rise to specific traits. Likewise, changes in receptor subtype or density within an area would change the postsynaptic effect achieved by any particular level of transmitter.

We can expect the state imaging of approach/avoidance to show changes in both the focus and magnitude of activation within distinct approach and avoidance goal-processing systems (Section 1.1). These changes in activation should depend both on changes in valuation affected by exchange rate factors, including loss aversion (Section 1.2), and on the location of the individual along spatial and temporal gradients (Section 1.3). When approach and avoidance goals are concurrently and similarly activated (i.e., the individual is in the range of intersection of their opposing goal gradients), the behavioral inhibition system will also be activated, in addition to the approach and avoidance systems (Section 1.3). With trait imaging, we can expect variation to be evident more globally across each system (and even between systems) and to be dependent on more global (e.g., hormonal) biological factors. However, the hierarchical organization of the systems means that the detection of trait variations may be as much a matter of detecting changes in the typical neural focus of activation within a system as it is a matter of detecting changes in the level of activation of a specific module within a system.

2. STATE NEUROIMAGING OF APPROACH, AVOIDANCE, AND GOAL CONFLICT

There is a vast amount of literature looking at the details of neural reactions to motivationally significant stimuli, choices, and responses. We will provide in this section only a brief, high-level overview, placing it in the context of the behavioral and neural foundations of goal-directed approach and avoidance provided in Section 1. We will focus on more global, systemic issues as a transition between the details of the key neural systems that we have already reviewed and attempt to assess their trait sensitivities, i.e., approach-prone and avoidance-prone personalities, which we will review in the next section.

Human imaging has not generally focused on approach or avoidance behavior as such. It has more often focused on "reward" or "punishment," which usually blend valuation and learning with approach or avoidance behavior. Human imaging has also seldom combined both negative and positive events with both negative and positive response contingencies. Further, in many cases, the neural response to different stimuli has been measured without any requirement to generate behavior. Where behavior is generated, it tends to be limited to pressing buttons, as there are strong technical reasons for limiting movement during functional magnetic resonance imaging (fMRI) and, although free-moving radio-transmitted EEG recording is available, the bulk of evoked potential and rhythmic EEG recording limits movement to reduce artifacts. Current imaging paradigms therefore make it difficult to identify signals that are specific to goal-directed approach or avoidance and are not confounded by other factors.

A further complication is that brain activation in relation to a motivationally significant event can reflect several different aspects of that event. Specifically,[48] valence (positive/neutral/negative) may be signaled independently of amount, salience (increasing with amount) may be signaled independently of valence, and value (valence x amount) may be signaled selectively for one valence with no value variation for the other valence.

The summary provided below largely ignores these complications. It lumps gain/reward with approach and loss/punishment with avoidance. It blurs the processing of upcoming goals with the evaluation of the outcomes of responding. Conversely, it focuses on differences in neural localization, or attempting to distinguish approach, avoidance, and goal conflict systems. This ignores the complication that there may be strong neural overlap between these different types of goal processing (with, e.g., lateral OFC, anterior insular cortex, and ACC showing valence-independent activations).[48] But there is also the likelihood that particular subregions may differentiate between approach, avoidance, and goal conflict in a way that generates a combined, blurred signal with current and relatively poorly localized imaging methods.

2.1 State Neuroimaging of Approach/Reward

As shown in Figure 6, goal-processing areas control behavior via links to the striatum,[36] and this is a major locus where the release of dopamine can alter future behavior. It will be significant for Section 3 that alterations in the dopamine system affect a broad range of motivated behaviors,[16] and so here we will focus first on the striatum and dopamine and then consider the goal-processing areas (Figure 7) on the output of which striatal dopamine can impact.

Imaging studies[36,49] show dopamine release linked to responses for secondary incentives as well as primary incentives, such as pleasant sounds or the simple presentation of food items to hungry participants. Striatal activation is observed prior to monetary choice and is maintained by gain more than loss (with value affecting dorsal but not ventral striatum and the latter preferentially reacting to gain as compared to loss outcomes). However, the striatal response is not mediated by the simple delivery of a positive or negative outcome but rather reflects whether the associated action is being reinforced. Additional data "strongly suggest that the human dorsal striatum is involved in reward processing, specifically learning and updating actions that lead to reward, rather than representing and identifying rewards, a function postulated to occur in frontal cortex."[49] The same appears to be true of the ventral striatum, which may sometimes code "reward prediction error."[36] Although reinforcement is important for determining the specifics of approach (and avoidance) behavior, these data provide no evidence that the basal ganglia are part of the specific systems controlling approach, to which we turn next.

The lowest level at which positive goals are known to be controlled is the lateral hypothalamus (Figure 7(B)). Imaging of the hypothalamus[50] via scalp EEG is impossible and via fMRI is difficult. It is less than 10 mm across, close to the sinuses, and contains different closely adjacent nuclei that may show opposite responses to a situation and therefore cancel out each other's signals. However, it has been studied to a small extent in the context of sexual arousal[51] and appetite control with results that suggest, consistent with Figure 7(B), that it "acts as a central gateway modulating homeostatic and nonhomeostatic drives."[50] Its activity is reduced by glucose (but not by either artificial sweetener or a nonsweet calorific solution) and this response is reduced in obese people and absent in type 2 diabetics. Its activity appears to be increased by

pictures of fattening food and is positively correlated to caloric intake.[50]

The amygdala is activated by food images in hungry participants (but not by nonfood images or in satiated participants) and by high-calorie items as opposed to low calorie items, with a stronger response and weaker amygdalar modulation of other areas to high calorie items in obese people.[50] (The hippocampus is also activated by food images—this will be dealt with in more detail in the section on goal conflict, below.) The "hunger hormone," ghrelin, also activates the amygdala.[50,52] The amygdala is also activated[36,53] by potential rewards, and its response decreases with reward devaluation. Compared with the ventral striatum, the response of the amygdala to reward shows rapid habituation, and the extent of activation does not differ from that produced by potential punishments when arousal level is controlled. It is also activated during sexual arousal.[51] These data are consistent with the view that the amygdala is important for the processing of positive goal stimuli and controls arousal for all motivational systems, both positive and negative.

The dorsal anterior cingulate cortex (dACC), as with the other areas we have considered, is activated by food relative to nonfood items; is more activated by high calorie items in obese people; and, together with other aspects of ACC, is involved in sexual arousal.[51] However, dACC (and dorsal prefrontal cortex/PFC) also engage in reward processing that is not directly linked to valuation (for example, supporting working memory for incentives that can then be used for outcome evaluation).[36] Indeed, "it has been proposed that the overall function of the dACC might involve the use of outcome, and particularly reward-related, information to guide action selection."[54] This outcome evaluation process, however, produces particularly clear activations (with fMRI and, particularly, EEG rhythmicity) when there is outcome conflict (i.e., when an expected reward is not delivered). Thus a major function of dACC (not inconsistent with simple outcome evaluation) appears to be outcome conflict monitoring.[54] As we discussed earlier, this outcome conflict (which should not be confused with goal conflict, see below) will generate a negative goal and will have all the effects expected of an explicit punishment. Interpretation of imaging results from dACC, therefore, has similar complications to the hypothalamus and amygdala, with both positive and negative information being processed in what appears to be closely adjacent areas.

OFC, as with the other areas we have considered above, is activated by visual food as opposed to nonfood images and shows a particularly clear differentiation in this response between fasted and sated states. It shows a high level of functional connectivity with the hypothalamus, increased activity in response to ghrelin,[52] and in general can be considered to be the most significant node in the networks encoding the rewarding value of stimuli.[50] Its posterior part is also activated during sexual arousal.[51,55] Its more anterior portions are activated by more abstract rewards, such as monetary gain.[55] Whereas medial regions respond to rewards (both in terms of magnitude and probability and adjusted for temporal discounting), more caudolateral regions respond to punishments and more rostromedial lateral regions appear to be involved in behavioral inhibition.[36,48] Medial OFC, together with adjacent medial frontal cortex, appears to be activated by the expectation of reward and is not activated by habitual stimulus-response learning.[53]

2.2 State Neuroimaging of Avoidance/Punishment

Some imaging studies focusing directly on defensive behavior have been undertaken and are considered in the following paragraph in relation to the entire system shown in Figure 7(A). Studies that investigate loss and punishment are then briefly discussed in relation to the studies of gain and reward reviewed in Section 2.1.

Volunteers in a virtual maze with a virtual predator (which could capture them and produce real pain via electric shock to a finger) showed activation of ventromedial PFC, rostral ACC and medial OFC, basolateral amygdala, central amygdala, and periaqueductal gray (PAG). This activation was strongest in more rostral structures to distal threat and more caudal ones to proximal threat—consistent with Figure 7(A).[56,57] Similarly, with simple aversive conditioning of a shock with a simple stimulus or a contextual stimulus, there was stimulus-related activation in the amygdala and hippocampus, respectively,[58] whereas with a virtual reality context, both amygdala and hippocampal activation were detected[59]—also consistent with Figure 7(A) (see also Section 2.3). In experimentally induced panic attacks, the PAG (and a range of other parts of the upper brain stem) and hypothalamus are activated, while medial PFC is not, and the ACC can become deactivated. This is consistent not only with the rostral-caudal shifts observed with decreasing defensive distance, but also with the idea that the strong activation of one level of the system will tend to reduce the involvement of other levels.[42] A PAG-hypothalamus-(amygdala)-premotor cortex network is activated by video clips of threatening actions,[60] while the anterior midcingulate responds to a range of stimuli that generate an intense negative effect, ranging from simple pain, through pain anticipation, the closeness of a spider to a foot, and emotionally charged words.[61] These results are all consistent with the notion of a hierarchically organized active avoidance system presented in Figure 7(A). Also consistent with the distinction between active avoidance (anxiolytic

insensitive) and BIS (anxiolytic sensitive), is the finding that benzodiazepine administration does not reduce pain-related activations in the brainstem, ACC, anterior and posterior insula, PFC, and other areas.[62]

The bulk of studies investigating loss or punishment in the same types of experiments as they investigate gain or reward involve the omission of the loss/punishment under conditions where it is difficult to distinguish the avoidance of danger from the approach to safety (Section 1). With this caveat, there is evidence for affectively negative activation in the amygdala, ACC, and more caudolateral aspects of OFC.[36,48] Explicit manipulation of the strength of unconditioned frustration (theoretically equivalent to punishment) activates PAG, amygdala, dACC and insula.[63] However, the areas controlling approach and avoidance may be difficult to distinguish.[48] With rewarding and punishing outcomes (as opposed to goal-oriented anticipation), activation can be virtually ubiquitous both with very little distinction between them and a capacity "for positive and negative outcomes to directly influence neural processing throughout nearly the entire brain."[64]

2.3 State Neuroimaging of Goal Conflict

Goal conflict is, in principle, more complex than simple approach or avoidance. But it has been subjected to much more extensive theoretical and neuropsychological analysis (Section 1.3), and critically, the actions of anxiolytic drugs have distinguished the BIS from simple approach and avoidance systems and so can be used to validate behavioral tests across species and dissect BIS-related (conflict) activations from those produced by a simple threat. However, it should be noted that one of the effects of BIS activation is to amplify avoidance tendencies.[1,2] Areas that are activated both by conflict and in simple avoidance tasks will clearly be involved in generating BIS-related output but cannot be definitively assigned as parts of the BIS itself, unlike those activated solely by conflict.

A recent, 2014, particularly explicit assessment of approach-avoidance conflict activation in humans used monetary tokens to generate approach and a virtual predator capable of causing the loss of a large number of tokens. Consistent with their BIS-theory-based hypotheses (see Figures 7 and 8), there was a linear correlation between the level (probability of loss) of imposed threat and the size of BOLD response in the left anterior hippocampus. There may also have been activation in the adjacent amygdala. Reliable (whole brain corrected) activations were also seen in right inferior frontal gyrus/insula, bilateral parahippocampal gyrus, and right fusiform gyrus. Interestingly, they confirmed the functional status of the hippocampal activations by showing that patients with a hippocampal lesion showed reduced approach-avoidance conflict in the same task.[65] Animal work has also linked contextual but not simple cued fear conditioning to the BIS. Consistent with this, the right amygdala, ACC, and insula (see also Section 2.4) were activated by a simple cue, as well as by the context during conditioning with a shock to the forearm as an unconditional stimulus. In contrast, the left hippocampus was activated only in the context condition.[58] Contextual conditioning (but without a simple cue as a contrast) with foot shock has also been reported to activate the *right* anterior hippocampus (as well as a range of other structures).[59] A potential predator threat has also been contrasted with direct predator interaction in a task with a virtual predator delivering delayed shocks. This contrast should specifically assess areas involved in the BIS, as it controls for more general threat detection and avoidance. Potential rather than direct predator interaction involved posterior cingulate cortex, bilateral hippocampus, hypothalamus, and amygdala (all consistent with Figure 7), as well as ventromedial PFC and subgenual ACC.[57]

Go/No-Go is a simple test of response inhibition with clear "involvement of a right prefrontal region, comprising the posterior part of the inferior frontal gyrus (IFG) and the adjacent part of the middle frontal gyrus (MFG) in the inhibitory process. …The anterior cingulate gyrus is also commonly activated … but has been attributed a more generic role of selective, executive attention and performance monitoring, which is consistent with the finding of its activation in particular during failed inhibition trials."[66] In contrast to more lateral regions of lateral OFC (Section 3), more rostromedial regions of lateral OFC appear to be involved in behavioral inhibition generally.[36,48]

Anxiolytic drug effects are generally consistent with the picture provided by simple conflict-related activations. Benzodiazepines, specific serotonin reuptake inhibitors (SSRIs), and, to some extent, pregabalin reduce threat-related activation in the amygdala, insula (see Section 2.4), and medial PFC.[67] Benzodiazepine reduced the activation generated by the anticipation of pain clearly in the right insula/inferior frontal gyrus/superior temporal gyrus but only marginally and nonsignificantly in the ACC, while not reducing any activations generated by pain itself.[62] Delta-9 tetrahydrocannabinol reduces Go/No-Go activation differences in the right inferior frontal gyrus and ACC.[66]

The most theoretically driven experiments attempting to image the BIS have involved the use of EEG. The detailed neuropsychological theory of the BIS[1,2] has, at its core, the fact that, without any false positive or negatives so far, all clinically effective anxiolytic drugs (including those that have no effect on panic or depression) reduce the frequency of hippocampal rhythmical slow activity (RSA, 5–12 Hz in the rat, likely somewhat lower in humans).[68]

"We developed a human homologue of rat RSA as a biomarker for BIS hyper-reactivity[/anxiety]. Hippocampal depth recording is impractical for assessing [BIS activity] in humans. However, in rats, rhythmicity in frontal cortex becomes coherent (phase-locked) with hippocampal RSA during risk assessment behaviours.[69] Since the hippocampus itself shows RSA even when it is not in control of behaviour, this outflow of RSA to PFC should be more predictive of BIS functional output and act as a better biomarker than hippocampal recording. We therefore searched for rhythmicity in human frontal cortex that was generated by goal (approach-avoidance) conflict and sensitive to anxiolytic drugs.

We measured human scalp EEG during approach, conflict, and avoidance, subtracting the average power in approach and avoidance from conflict to measure *goal – conflict-specific rhythmicity* (GCSR). We found GCSR at a right frontal cortex site (F8).[70,71] Right frontal cortex (particularly the inferior frontal gyrus) controls stopping[72–75] (a major output of the BIS) in the Stop Signal Task (SST)[76]. …We used the SST to extract GCSR from F8 and found that this correlated positively with both trait anxiety and neuroticism.[77] Critically, we later showed that F8 GCSR was reduced by both benzodiazepine and 5HT1A drugs[78] that share, in the clinic, only BIS and not [avoidance] or antidepressant actions. So, right frontal GCSR elicited in the SST task in humans is pharmacologically homologous to RSA elicited by electrical stimulation in rats." McNaughton[45], p. 140

2.4 "A Link between the Systems"—State Neuroimaging of the Insula

In the previous sections, we have mentioned only in passing one structure that is routinely activated in tasks involving goals:[48,53] the insula. The previous sections reviewed systems that are likely to be specifically involved in goal-directed approach, avoidance, or conflict and that are likely to be distinguished either in terms of the large-scale structures involved (e.g., hippocampus) or in terms of the specific nuclei involved within a structure (e.g., within the amygdala). The insula is a "distinct, but entirely hidden lobe… (mostly) reciprocally connected with the amygdala, and with many limbic and association cortical areas, and is implicated in an astonishingly large number of widely different functions, ranging from pain perception and speed production to the processing of social emotions."[79] It acts as a major network hub,[80,81] which can be viewed as a "limbic integration cortex."[82] Rather than specifically supporting approach, avoidance, conflict, or any more complex aspect of goal processing, the anterior insula in particular[81] appears to act as a "link between the systems,"[83] allowing a mixed readout from the motivational activations of all of them.

The anterior insula appears to be involved in at least the initial aspects of goal processing, particularly valuation. Ghrelin (see also Section 2.1) activates anterior insula.[52] Reward anticipation activates the anterior insula more than reward outcome.[84] The anterior insula has activations related to the subjective value of rewards independent of type,[55] to sexual arousal,[85] to the values of losses,[48] and to the proximity of threat.[86] Variations in loss aversion between people are mirrored by valuation-related differences in activation to gain and loss in the insula.[20] Risk, in many different forms, activates the anterior insula,[87] and risk averse people show stronger anterior insula responses in anticipation of high risk gambles.[88]

Overall, the anterior insula, despite some parcelation and differentiation, appears to be "instrumental in integrating disparate functional systems involved in processing affect, sensory-motor processing and general cognition and is well suited to provide an interface between feelings, emotion and cognition."[89] Suggested integrative functions include the following: (a) "mediating dynamic interactions between other large-scale brain networks involved in externally oriented attention and internally oriented or self-related cognitions… [so as to mark salient] events for additional processing and initiate appropriate control signals … to guide behavior";[90] and (b) integrating "different qualities into a coherent experience of the world and setting the context for thoughts and actions."[83] It appears, then, to be an area where the outputs of approach, avoidance, and conflict systems can become integrated rather than being a part of any one of those systems or having separate zones within it dedicated to each.

Despite its apparent role in integrating across the motivational systems, there may be reason to see the insula as particularly important for anxiety in general (the BIS in particular). Its likely role in monitoring higher levels of the motivational systems and "initiating appropriate control signals" clearly includes involvement in anxious anticipation,[86] and the equivalent of the conflict-monitoring and resolution functions of the BIS. Like the BIS, its dysfunction has been specifically linked to phobic and anxious disorders.[91] It is also closely associated with the right inferior frontal gyrus, which makes a major contribution to response inhibition[92] in distinction to mesial PFC, which is more involved in error detection,[93] and to ACC, which is more involved in outcome conflict monitoring.[54,94]

The insula also contains both benzodiazepine[95] and 5HT1A[96] receptors. An indication of their likely function is given by the fact that the benzodiazepine, midazolam, reduces anterior insula activation by anticipated pain but not by pain itself.[62] Likewise, benzodiazepines and SSRIs (and to some extent pregabalin) reduce threat-related activation in the insula.[67] The presence of direct targets for different types of anxiolytic in the insula raises the possibility that it may contain frontal components of the BIS. (The neuropsychology of the BIS, see Figure 7, has not been worked out in detail for the frontal cortex.)

However, the insula appears to go beyond simple goal conflict even in its involvement in inhibitory control,[32] and it has been proposed as part of "a ventral system, including the amygdala, insula, ventral striatum, ventral ACC, and PFC, for identification of the emotional significance of a stimulus, production of affective states, and automatic regulation of emotional responses [and not part of] a dorsal system, including the hippocampus, dACC, and PFC, for the effortful regulation of affective states and subsequent behavior."[97,98] On this view, it would be quite distinct from the BIS, which has the hippocampus as its most important node.

3. TRAIT NEUROIMAGING OF APPROACH, AVOIDANCE, AND GOAL CONFLICT

Psychological traits describe a variation in the likelihood of being in particular classes of states, and much of this variation is assumed to be due to differences in the sensitivities or strengths of the systems that generate the relevant states in response to appropriate eliciting stimuli.[99] Traits that reflect variation specifically in approach or avoidance behavior, therefore, are hypothesized to stem from variation in the systems described above as underlying approach- and avoidance-related states. Investigating this hypothesis requires testing whether traits are associated with relevant neurobiological parameters.

For three reasons, trait research is more difficult than research designed to understand the nature of approach and avoidance systems as such. First, much larger sample sizes are required in order to have sufficient statistical power to test associations with individual differences, relative to the samples required for comparing the operation of a particular brain system under different conditions in the same individuals. Second, an additional type of measure must be included in the research—that is, measures of traits, which must be validated as measuring a reasonably stable pattern of behavior over an extended period of time. Third, neurobiological parameters that can adequately explain trait variation must themselves be reasonably stable over time. This requires proof that measures of those parameters are sufficiently trait-like.

The field of personality neuroscience is sufficiently new that at least two of those three requirements have not been met in much of the existing scientific literature. First, many MRI and positron emission tomography (PET) studies have used such small samples that their findings are of little evidentiary value. This is because underpowered samples not only increase the likelihood of false negatives, in which a real effect cannot be detected as statistically significant, they also increase the proportion of significant findings that are false positives, in which an effect that has been detected as significant does not in fact exist. The latter problem is a direct result of sampling variability—the smaller the sample, the more likely it is to be so unrepresentative of the general population as to yield, by chance, a parameter value large enough to be significant when the true value is, in fact, close to zero (or even far from zero in the opposite direction).

Unfortunately for the study of individual differences, correlations are particularly susceptible to outliers, and close to 200 participants are necessary to achieve 80% power to detect the average effect in personality research ($r = 0.21$,[100] which is similar to the typical effect size in psychology more generally).[101] In the last few years, sample sizes in personality neuroscience have been increasing, but there is still relatively little trustworthy existing research to review. The median sample size in a random sample of 241 neuroimaging papers published after 2007 was 15.[102] Many of these were studies of within-person effects (though even for within-person research, 15 is typically inappropriately small), but many correlational studies have also been published with samples smaller than 20, and these should not be trusted.

Additionally, most neural variables have not been examined in terms of their test-retest reliability. If a measure is not reliable as an index of a stable parameter, then it is not trait-like and, therefore, probably cannot be systematically linked to any given trait, even if the system being measured is genuinely related to that trait. Some research has begun on the test-retest reliability of MRI assessments, and additional work in this vein will be crucial for the advancement of personality neuroscience.[103–105]

In contrast to neuroimaging variables, trait measures, especially questionnaire measures, are much more likely to have been validated as having sufficient test-retest reliability. Still, questionnaire measures have limitations of their own. Various biases may influence the way that people respond to questionnaires, and the best questionnaire assessment can be achieved by including peer ratings in addition to self-ratings.[106,107] Other methods of trait assessment exist, using decision-making or behavioral tasks instead of questionnaires, but these have been much less extensively developed. One example of a task that has been validated as having trait stability is a decision-based assessment of temporal discounting.[108,109]

One obvious limitation of all psychological trait measures is that they do not reveal the neurobiological systems underlying the behavior they assess. For this reason, labeling questionnaires with the names of neural systems is potentially misleading. The widely used BIS/BAS scales,[110] for example, do not measure and have not been tested against the sensitivity of BIS (see Section 2.3) and BAS as neural systems. They assess patterns of

behavior and emotional experience that their authors hypothesized to be linked to BIS and BAS sensitivity. At this early stage of personality neuroscience, we should not assume the very hypotheses that need to be tested. The question of how the approach, avoidance, behavioral inhibition, and other neural systems are responsible for the variation in traits is precisely what the field must strive to discover.

Neuroimaging research to test whether various traits are related to these neural systems has typically been carried out using questionnaire measures of traits. Two major approaches have been used to develop personality questionnaires: the theoretical approach and the empirical approach. In the former, one starts with a trait construct identified through observation and theory and attempts to develop items rationally. These items are then typically winnowed, through psychometrics, so as to be sufficiently unidimensional, and the scale is often validated by showing convergent and discriminant validity with other scales and by demonstrating that it predicts some hypothetically relevant behavior. This is the approach that was used to develop the BIS/BAS scales, for example.[110] The major limitation of this approach is that one's theory and intuitions about what items will be good indicators of the construct in question may be wrong. One may develop a scale that is reliable psychometrically but lacks validity (i.e., that does not adequately measure the construct intended) and predicts seemingly relevant behaviors for reasons other than those dictated by the guiding theory. For example, the Autonomic Perception Questionnaire does not relate to people's actual individual capacity to perceive their heart rate.[111]

In empirical questionnaire development, in contrast, one starts with a broad pool of variables (items or scales), without a priori hypotheses regarding exactly what trait dimensions are measured. Factor analysis is then used to determine the major dimensions of covariation among the variables. With a sufficiently broad and unbiased pool of variables (difficult to achieve in practice), this approach is theoretically capable of addressing one of the central questions of personality research, namely which traits tend to manifest together in the same people. This approach is crucial for understanding the structure of personality traits, and it has led to the widely used Five-Factor Model or Big Five,[112,113] sometimes extended to include a sixth factor.[114] Such models are important because they identify the major dimensions of personality, but they have the serious limitation that they reveal nothing about the sources of those dimensions. Considerable research at lower (e.g., neural) levels is subsequently needed to understand what causes the traits in each dimension to covary.[115,116]

A third approach, which has so far been little used in personality neuroscience but is a promising alternative to the standard theoretical and empirical approaches, is the criterion approach. This approach would start with a well-validated biomarker (a trait-like neural parameter) and then identify questionnaire items most strongly associated with that variable. This is already possible with the BIS.[45,117] A scale developed on this approach would not only provide new insights regarding the behavioral and experiential correlates of the biomarker, it would also allow the best possible questionnaire measurement of a neural parameter. Importantly, it is theoretically possible that some key, stable, biological source of individual differences could be identified first, and the nature of its emergent psychological construct determined only later.

3.1 Neuroimaging and Approach Traits

Both theoretically and empirically derived scales have been used in neuroimaging research. Although approach and avoidance tendencies have not been measured by questionnaires in such a way as to disentangle motivation from valuation, we can nonetheless identify traits related to these motivational factors. To begin with those related to approach, the most commonly studied traits are those in the extraversion family. Extraversion is one of the Big Five dimensions, reflecting the shared variance of more specific traits, such as gregariousness, assertiveness, enthusiasm, talkativeness, activity level, and excitement-seeking. Though often expressed in the social domain, extraversion has been hypothesized to reflect sensitivity to reward more generally, with the tendency to approach positive goals as an important component of the trait.[115,116,118] The BAS scale[110] shows reasonable convergent validity with extraversion and can be included in this family of traits.[119,120]

Research on extraversion is covered in more depth in Chapter 6, but we will briefly review some of the studies that have linked extraversion and related traits to components of the BAS. The most compelling evidence comes from studies showing that people high or low on extraversion respond differently to pharmacological manipulation of the dopaminergic system.[121–129] A number of fMRI studies have reported that extraversion or the BAS scale is associated with neural activation in response to emotionally positive or rewarding stimuli, often in approach-related brain regions, including those in Figure 7.[130–133] However, all of the studies just cited used samples smaller than 20, meaning that they are of little evidentiary value. In the future, higher-powered fMRI studies should be one of the most powerful methods for testing the hypothesis that variation in the approach system underlies traits in the extraversion family.

Structural MRI studies have begun to use larger sample sizes, and several of them have found that extraversion is associated with volume in the ventromedial

PFC/OFC.[134–137] Other studies, however, have not replicated these findings.[104,138–140] However, these studies have varied in their methods and populations studied, which could account for some of the inconsistencies. More large primary studies, as well as meta-analyses, will be needed to provide convincing tests of this and other effects in personality neuroscience. Associations of extraversion with other brain regions have been even more inconsistent in structural MRI studies. One study worth mentioning because of its large sample size ($N = 486$) reported that an extraversion-related scale (positive emotionality from the Multidimensional Personality Questionnaire) was positively associated with left amygdala volume.[141]

Resting EEG hemispheric asymmetry, in which the one frontal lobe of the brain is more active than the other, is another neural parameter that has been linked to motivation.[142] Controversy exists, however, regarding whether left versus right bias corresponds to approach versus avoidance or to goal-directed activity (including both approach and active avoidance) versus goal conflict and passive avoidance.[143] A number of studies have found that extraversion is related to left-dominant asymmetry, but failures to replicate have been reported as well, and a meta-analysis found no evidence for the effect.[144] Nonetheless, although EEG frontal asymmetry at rest may not be generally related to trait approach, it is possible that frontal asymmetry is related to approach-related traits in contexts that evoke approach motivation. In an all-male sample, the BAS scale was found to predict resting-state asymmetry only for participants interacting with a female experimenter whom they rated as attractive[129]—such findings point to further complexities in the neuroimaging laboratory that should not be ignored. Another much smaller study found a similar effect: a trait measure of approach-related positive affect was associated with asymmetry only under the condition of a positive mood manipulation, but not in negative or neutral-mood conditions.[145] The possibility that extraversion is associated with asymmetry only in certain contexts would be consistent with the definition of traits as tendencies to respond in particular ways to particular classes of stimuli. Without the presence of a relevant stimulus, the trait may not be manifested, and individual differences in behavior or neural activity may not be apparent.

Gray[24] originally hypothesized that the trait most associated with BAS sensitivity is impulsivity, but more recent research suggests extraversion is probably more specifically related to BAS sensitivity.[118,120,146,147] Nonetheless, some forms of impulsivity (particularly those related to extraversion) appear to be linked to the neural systems involved in approach. Impulsivity is "the tendency to act on immediate urges, either before consideration of possible negative consequences or despite consideration of likely negative consequences."[148] Because any instance of impulsivity requires both the presence of an impulse to act and a failure to constrain that impulse, variation in both bottom-up impulse systems related to approach and avoidance, as well as top-down constraint systems in the PFC, may lead to different types of impulsivity.

Two types of impulsivity appear to be importantly related to approach behavior: (1) the tendency to act quickly to approach potential reward, with little deliberation or premeditation and (2) the tendency to take risks for the sake of excitement or novel experience. Both of these traits have been linked to dopaminergic function, using PET imaging to show that they reduced D2 binding in the midbrain, which in turn predicts greater dopaminergic release in the striatum in response to amphetamine.[149,150] A lack of deliberation has also been shown, in fMRI, to predict increased ventral striatal activity in response to cues of reward.[151,152] (For further discussion of impulsivity, see Chapter 8.)

3.2 Neuroimaging and Avoidance and Goal Conflict Traits

Personality research has tended not to distinguish clearly between traits reflecting individual differences in active avoidance versus those that reflect differences in processing goal conflict. This is probably due to the fact that activation of the BIS leads to increased arousal of active avoidance systems and biases motivation toward avoidance, as well as to the fact that certain neuromodulators, including serotonin and noradrenaline, influence both systems. In psychometric research, trait measures of anxiety, depression, and other traits related to passive avoidance covary strongly with trait measures of fear, panic, irritability, and other emotional forms of active avoidance. Together, the tendency to experience all of these negative emotional states (and related cognitive, motivational, and behavioral states) constitutes the broad Big Five dimension labeled neuroticism. Neuroticism is the major risk factor for psychopathology.[153]

Many theoretically derived trait measures fall within the neuroticism family, including Cloninger's Harm Avoidance,[154] various measures of trait anxiety,[155] and Carver and White's BIS scale.[110] (For further review of neuroimaging related to traits in this family, see Chapter 7.) The fact that a scale is labeled an "anxiety" scale does not mean it measures anxiety in the specific sense, related to the BIS, we have used in this chapter, and, due to the ambiguity of the concept, it may not measure "anxiety" in a more general sense either. Neuroticism appears to have two major subfactors, one reflecting anxiety, depression, and other internalizing problems, the other reflecting irritability, anger, emotional lability, and the tendency to get upset easily.[156] Scales in the neuroticism family tend to measure either the first factor or

a blend of both factors. Only rarely do they target more specific facets capable of distinguishing, for example, between anxiety and depression. A recent attempt to develop separate scales reflecting approach, avoidance, and conflict sensitivities, using the theoretical method, was carried out by Corr and Cooper.[157]

Gray and McNaughton[1] posited that neuroticism reflects the joint sensitivity of behavioral inhibition and avoidance systems, implying that it should be influenced by the neuromodulators serotonin and noradrenaline. This hypothesis has been supported for serotonin using a variety of methods, including genetics and pharmacological manipulation, but also neuroimaging:[115] several PET studies have found that neuroticism predicts variation in serotonin receptor or transporter binding.[158–160] Only the most recent of these used a sample large enough to be particularly informative, however, and additional studies are necessary. Less evidence exists linking noradrenaline to neuroticism, but it remains a promising hypothesis.[161,162]

A number of fMRI studies have reported that neuroticism predicts neural responses to aversive stimuli in relevant brain areas from Figure 7, but most of these have used samples so small as to preclude confidence in their results. Of 21 samples in a recent meta-analysis of these effects,[163] only 7 of them were larger than 25, and only 1 was larger than 60. Unfortunately, meta-analysis is not a panacea for the problems created by underpowered samples, as meta-analytic conclusions are likely to be biased by their inclusion. Nonetheless, it is worth noting that the meta-analysis in question found neuroticism to be associated with neural activity only in aversive relative to neutral conditions and not in positive relative to neutral conditions, which is encouraging for the theory that neuroticism reflects the major manifestation of both active and passive avoidance motivation in personality; however, it does little to throw much light on the nature of this association.

Many theoretical accounts of the neurobiology of neuroticism highlight a central role for the amygdala, which is unsurprising given its role in the mobilization of anxiety and fear. Although the meta-analysis by Servaas and colleagues[163] did not implicate the amygdala, some larger fMRI studies have found associations between avoidance traits and amygdala reactivity to aversive stimuli. Unfortunately, these studies have used a variety of different methods and experimental paradigms, so it remains difficult to draw any firm conclusions. Neuroticism or trait anxiety has been found to predict: (1) a slower decrease in amygdala activity after viewing aversive images;[164] (2) greater amygdala activity in response to aversive images, but only in people generally lacking in social support;[165] (3) reduced synchrony between amygdala and other limbic regions, especially in the PFC;[166] and (4) reduced synchrony between the left amygdala and the medial PFC when viewing negative versus neutral emotion faces, but increased synchrony between these structures in the right hemisphere.[167] The last two findings in this list raise the possibility that functional interactions between the amygdala and regions of the frontal cortex may be important in determining levels of neuroticism.

One fMRI study reporting a link between neuroticism and neural activity in the amygdala is worth mentioning, despite having a sample of only 17, because it used an innovative method to distinguish between valuation and motivation.[168] Participants viewed positive, negative, and neutral images and were required either to approach them (by pressing a button that enlarged the image, creating the illusion of approach) or to avoid them (by pressing a button that reduced the image in size). The study found that one of the two major subfactors of neuroticism (related to anxiety and depression) predicted amygdala reactivity to approach relative to avoidance (regardless of stimulus valence), whereas the other (related to anger and lability) predicted amygdala reactivity to negative relative to neutral and positive stimuli (regardless of motivational direction).

The apparent importance of the amygdala for neuroticism in terms of brain function is consistent with structural neuroimaging studies that have shown traits in the neuroticism family to be related to increased amygdala volume.[169,170]. As with approach-related traits, however, there has been little consistency in studies of the association of traits in the neuroticism family with the volume of specific brain regions, even as sample sizes have increased, and other studies have not found amygdala volume to be associated with these traits.[135,171,172] Some of the inconsistencies here may reflect methodological differences, given differences in the questionnaires used, and differences in MRI analysis. Refreshingly, in this case, a nearly definitive study has been carried out in a sample of over 1000 people, which found that neuroticism scores (based on the average of several commonly used questionnaire measures) were indeed positively correlated with amygdala volume (after controlling for age, sex, and total brain volume), albeit very weakly ($r = 0.1$, i.e., accounting for only 1% of the variance[103]). Only one other subcortical structure, the hippocampus, was also significantly correlated with neuroticism ($r = 0.1$). These findings are important both because they confirm that neuroticism is associated with the two subcortical structures most strongly theoretically implicated in the trait, and also because they suggest an explanation of inconsistent findings. The structural effects studied are weak enough that even samples that are very large by neuroimaging standards may be underpowered to detect them.

In addition to demonstrating the positive association of neuroticism with both amygdala and hippocampal

volume, Holmes and colleagues[103] found that neuroticism was negatively associated with the thickness of a region of the rostral ACC and the adjacent medial PFC. Further, among the individuals scoring highest in neuroticism (more than one standard deviation above the mean), cortical thickness in this region was negatively correlated with amygdala volume (whereas they were unrelated in the rest of the sample). These additional findings are consistent with the theory that neuroticism results not only from functional sensitivity of subcortical structures involved in avoidance, but also from impaired regulation of these structures by higher-level control systems. Also consistent with this theory are diffusion tensor imaging studies (which assess the structure of white matter tracts) showing that traits in the neuroticism family are associated with reduced integrity of tracts connecting cortical and subcortical regions.[138,173–175]

One additional broad pattern has appeared in structural neuroimaging research on neuroticism: the trait appears to be negatively related to global measures of brain volume, such as volume of cerebral gray matter, ratio of brain volume to intracranial volume, and total brain volume.[138,140,176,177] This association of neuroticism with reduced brain volume has been hypothesized to reflect cell death due to the potentiation of excitotoxic processes by the stress hormone cortisol.[177] Several studies have shown that neuroticism is associated with elevated basal levels of cortisol.[178–181]

The last finding we will consider in relation to avoidance traits is the complement to the finding that extraversion may be associated with hemispheric asymmetry in EEG. Considerable research has shown that traits in the neuroticism family predict greater right relative to left neural activity in the frontal lobes when viewing stimuli or while at rest.[182,183] Similarly, a recent study used near-infrared reflection spectroscopy, a technique that uses light to measure regional cerebral oxygenated hemoglobin, to demonstrate that cerebral blood flow is increased in the right frontal lobe in individuals high on neuroticism during anticipation of a shock.[184] It would be a mistake, however, to think that all traits in the neuroticism family are associated with right-dominant frontal asymmetry. The effect appears to be limited to traits involving passive avoidance, such as anxiety and depression. In contrast, traits of anger-proneness and hostility are associated with greater left-dominant frontal asymmetry,[185–187] further supporting the hypothesis that the right hemisphere is specialized for processing goal conflict, rather than for all avoidance-related processes.

3.3 Future Directions for Trait Research

There are a number of aspects of current trait research on the neuroimaging of approach, avoidance, and conflict that are clearly unsatisfactory. Most obvious is the fact that, particularly in the strict senses defined in Section 1, there has been no neuroimaging that can be unambiguously linked to traits specifically reflecting approach, or avoidance, or conflict. A conflict-specific biomarker has recently been identified (and correlates moderately with neuroticism and trait anxiety)[77] but has not yet been used to identify specific related trait components. Trait scales related to positive affect (extraversion, etc.) and negative affect (neuroticism, harm avoidance, etc.) have been shown to have neural correlates, but none of these are pure measures of approach, avoidance, or conflict sensitivity. It is clear that neuroticism is not pure avoidance sensitivity or pure conflict sensitivity, although it appears linked to both of these factors and to others (e.g., depression) as well. Similarly, extraversion encompasses behaviors reflecting not only the tendency to approach but also positive emotional tendencies having to do with the enjoyment of rewards after they are received.

We believe there are five main steps that need to be taken to improve research on the functional neuroimaging of approach and avoidance traits: (1) to take account of the detailed knowledge derived from both animal and human work about the approach, avoidance, and conflict systems (Section 1.1–1.3) to develop more specifically targeted experimental tasks, using carefully designed contrasts between sets of conditions; (2) to test more focused anatomical hypotheses specified by theory, using carefully designed regions of interest (Section 1.4–1.5); (3) to take advantage of related state research (Section 2) to develop appropriate anchoring biomarkers; (4) to collect samples large enough for good research on individual differences—over 100 at a minimum, preferably over 200 (while recognizing that such samples may still be too small to detect some effects of interest); and (5) to ensure that the appropriate level in the trait hierarchy is being matched to the appropriate aspect of neural organization, taking into consideration that an observed association with one trait might, in reality, be either more specific (with a facet of the trait in question) or more general (with a trait at a higher level of the hierarchy).

4. FROM BASICS TO STATES AND TRAITS: ASSESSING APPROACH, AVOIDANCE, AND GOAL CONFLICT

Our analysis of the basics of approach, avoidance, and goal conflict shows that care must be exercised when using complex combinations of motivational stimuli and complex paradigms. Variations in valuation, such as loss aversion, differential effects of approach and avoidance gradients, direct interactions between approach and avoidance systems, and the asymmetric impact of goal conflict on avoidance relative to approach, must all be

taken into account when interpreting many of the paradigms currently used. However, in principle, state analysis of these systems is straightforward.

One simplifying step is to use money as the source of motivation. Organizations that find work for students and other casual workers can supply participants with a hunger for money sufficient to make them willing to work for the local minimum wage. Importantly, loss of money from an existing store can then be used as a motivator, with the knowledge that its external value is the same as the gain of the same amount of money used as a positive motivator. As shown in Figure 3, gain and loss can be presented or omitted to generate approach or avoidance. The amounts of gain and loss can then be varied parametrically to allow mathematical extraction, separately, of the contribution of gain/loss sensitivity differences and of approach/avoidance sensitivity differences. Using these methods, loss aversion and approach preference have been demonstrated.[188]

For neuroimaging, it is also important to use designs that allow the calculation of appropriate contrasts. If one wishes to image goal conflict activation, one must accept that gain, loss, approach, avoidance, and other systems will all necessarily be activated when approach-avoidance conflict is being generated. To deal with this requires the use of at least three conditions. For example, with conditions that deliver two alternatives with a 50% probability on any trial, one could have: (1) net gain (−10c, +20c); (2) conflict (−15c, +15c); and (3) net loss (−20c, +10c). A contrast of neuroimaging activation in condition 2 against the average of condition 1 and condition 3 would assess goal conflict-specific activation while eliminating the effects of external value (15c = (10c+20c)/2) and controlling for effects of factors such as risk. In practice, because of loss aversion, to statistically eliminate the effects of gain, loss, approach, and avoidance, when assessing conflict, one would need the ratio of gain/loss amounts tailored to each individual's degree of loss aversion. Additional conditions would allow the separation of the effects of gain from the effects of loss and effects of approach from the effects of avoidance.[188]

For those interested in goal gradients (Figures 2 and 4), existing virtual reality maze paradigms (see Section 2.2) or even simpler runway analogues could be used. These have already demonstrated effects related to distance from a "predator," as well as differences between simple anticipation of shock and the response to actual shock delivery. Combined with the presentation of money (to selected money-hungry participants), these virtual reality paradigms allow manipulation of the full gamut of parameters that have previously been used in animal behavior tests.

It is tempting, in the imaging of personality, to select questionnaires that have been designed, in theory, to tap into specific neurobiological functions (e.g., scales purporting to measure Gray's Behavioral Inhibition System) but that have not in fact been neurobiologically validated. However, as we noted earlier, the nascent neuroscience of personality should not assume the very hypotheses that need to be tested. Psychologists' presuppositions about which neural systems are responsible for any given trait, as measured by a questionnaire, may well be wrong. With approach, avoidance, and conflict, we are dealing with primordial biological systems whose elements have evolved to fulfill system-specific purposes. The state activation of these systems can be, and has been, assessed directly, with specific components extractable through appropriate contrasts. These specific components of neural state activation provide, we would argue, the best basis both for assessing personality-related variation in activation and for deriving questionnaire scales or other measures of approach, avoidance, and goal conflict traits, using the criterion approach described in Section 3. How the sensitivities of the approach, avoidance, behavioral inhibition, and other neural systems give rise to variation in traits is the key question that the field must strive to solve. A genuinely neuroscientific approach will provide a solid basis for future attempts to understand the contribution of these fundamental neural systems to traits such as extraversion, neuroticism, impulsivity, and others.

References

1. Gray JA, McNaughton N. *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System*. 2nd ed. Oxford: Oxford University Press; 2000.
2. McNaughton N, Corr PJ. A two-dimensional neuropsychology of defense: fear/anxiety and defensive distance. *Neurosci Biobehav Rev*. 2004;28:285–305.
3. McFarland D. *The Oxford Companion to Animal Behaviour*. Oxford: Oxford University Press; 1987.
4. Hinde RA. *Animal Behaviour*. New York: McGraw-Hill Book Company; 1966.
5. Cahill L, McGaugh JL, Weinberger NM. The neurobiology of learning and memory: some reminders to remember. *Trends Neurosci*. 2001;24(10):578–581.
6. Towe AL, Luschei ES. Preface. In: Towe AL, Luschei ES, eds. *Motor Coordination*. New York: Plenum Press; 1981:vii–viii.
7. Miller NE. Experimental studies of conflict. In: Hunt JM, ed. *Personality and the Behavioural Disorders*. New York: Ronald Press; 1944:431–465. [Cited by Kimble, 1961].
8. Amsel A. Frustrative nonreward in partial reinforcement and discrimination learning: some recent history and a theoretical extension. *Psychol Rev*. 1962;69:306–328.
9. Amsel A. *Frustration Theory: An Analysis of Dispositional Learning and Memory*. Cambridge: Cambridge University Press; 1992.
10. Amsel A, Roussel J. Motivational properties of frustration. I. Effect on a running response of the addition of frustration to the motivational complex. *J Exp Child Psychol*. 1952;43:363–368.
11. Adelman HM, Maatsch JL. Learning and extinction based upon frustration, food reward, and exploratory tendency. *J Exp Psychol*. 1956;52:311–315.

12. Gray JA. *The Psychology of Fear and Stress*. London: Cambridge University Press; 1987.
13. Kahneman D, Tversky A. Prospect theory: an analysis of decision under risk. *Econometrica*. 1979;47:263–291.
14. Novemsky N, Kahneman D. The boundaries of loss aversion. *J Mark Res*. 2005;42:119–128.
15. Tversky A, Kahneman D. Loss aversion in riskless choice: a reference dependent model. *Q J Econ*. 1991;106:1039–1061.
16. Berridge KC. Motivation concepts in behavioral neuroscience. *Physiol Behav*. 2004;81:179–209.
17. Berridge KC. Food reward: brain substrates of wanting and liking. *Neurosci Biobehav Rev*. 1996;20:1–25.
18. Gray JA. *Elements of a Two-process Theory of Learning*. London: Academic Press; 1975.
19. Brown JS. Gradients of approach and avoidance responses and their relation to level of motivation. *J Comp Physiol Psychol*. 1948;41:450–465.
20. Tanaka SC, Yamada K, Yoneda H, Ohtake F. Neural mechanisms of gain–loss asymmetry in temporal discounting. *J Neurosci*. April 16, 2014;34(16):5595–5602.
21. Miller NE. Liberalization of basic S-R concepts: extensions to conflict behaviour, motivation and social learning. In: Koch S, ed. *Psychology: A Study of a Science*. New York: Wiley; 1959:196–292. [Cited by Gray, 1975].
22. Kimble GA. *Hilgard and Marquis' Conditioning and Learning*. New York: Appleton-Century-Crofts; 1961.
23. Gray JA. Drug effects on fear and frustration: possible limbic site of action of minor tranquilizers. In: Iversen LL, Iversen SD, Snyder SH, eds. *Handbook of Psychopharmacology Vol. 8. Drugs, Neurotransmitters and Behaviour*. Vol. 8. New York: Plenum Press; 1977:433–529.
24. Gray JA. *The Neuropsychology of Anxiety: An Enquiry in to the Functions of the Septo-hippocampal System*. Oxford: Oxford University Press; 1982.
25. Bailey CJ, Miller NE. The effect of sodium amytal on an approach-avoidance conflict in cats. *J Comp Physiol Psychol*. 1952;45(4):205–208.
26. Barry H, Miller NE. Effects of drugs on approach-avoidance conflict tested repeatedly by means of a telescope alley. *J Comp Physiol Psychol*. 1962;55(2):201–210.
27. Razrin G. *Mind in Evolution*. Boston: Houghton Mifflin; 1971. [cited by Gray, 1975].
28. Hebebrand J, Friedl W, Breidenbach B, Propping P. Phylogenetic comparison of the photoaffinity-labeled benzodiazepine receptor subunits. *J Neurochem*. 1987;48:1103–1108.
29. LeDoux JE. Emotion, memory and the brain. *Sci Am*. 1994;270: 50–59.
30. Dawkins R, Krebs JR. Arms races between and within species. *Proc R Soc Lond B Biol Sci*. 1979;205:489–511.
31. Haegelen C, Rouaud T, Darnault P, Morandi X. The subthalamic nucleus is a key-structure of limbic basal ganglia functions. *Med Hypotheses*. 2009;72:421–426.
32. Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev*. 2009;33:631–646.
33. Haber SN, Calzavara R. The cortico-basal ganglia integrative network: the role of the thalamus. *Brain Res Bull*. 2009;78(2–3): 69–74.
34. Kolb B, Whishaw IQ. *Fundamentals of Human Neuropsychology*. San Francisco: W. H. Freeman; 1980.
35. Bear MF, Connors BW, Paradiso MA. *Neuroscience: Exploring the Brain*. Baltimore: Williams and Wilkins; 1996.
36. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*. January 2010;35(1):4–26.
37. Blanchard RJ, Flannelly KJ, Blanchard DC. Defensive behaviors of laboratory and wild *Rattus norvegicus*. *J Comp Psychol*. 1986;100(2):101–107.
38. Blanchard RJ, Blanchard DC. Antipredator defensive behaviors in a visible burrow system. *J Comp Psychol*. 1989;103(1):70–82.
39. Blanchard RJ, Blanchard DC. An ethoexperimental analysis of defense, fear and anxiety. In: McNaughton N, Andrews G, eds. *Anxiety*. Dunedin: Otago University Press; 1990:124–133.
40. Blanchard RJ, Blanchard DC. Anti-predator defense as models of animal fear and anxiety. In: Brain PF, Parmigiani S, Blanchard RJ, Mainardi D, eds. *Fear and Defence*. Chur: Harwood Acad. Pub.; 1990:89–108.
41. Graeff FG. Neuroanatomy and neurotransmitter regulation of defensive behaviors and related emotions in mammals. *Braz J Med Biol Res*. 1994;27:811–829.
42. Graeff FG, Del-Ben CM. Neurobiology of panic disorder: from animal models to brain neuroimaging. *Neurosci Biobehav Rev*. 2008;32:1326–1335.
43. Shizgal P, Fulton S, Woodside B. Brain reward circuitry and the regulation of energy balance. *Int J Obes*. 2001;25:S17–S21.
44. Mahler SV, Berridge KC. Which cue to "want?" Central amygdala opioid activation enhances and focuses incentive salience on a prepotent reward cue. *J Neurosci*. May 20, 2009;29(20): 6500–6513.
45. McNaughton N. Development of a theoretically-derived human anxiety syndrome biomarker. *Trans Neuro*. 2014;5(2):137–146.
46. McNaughton N. Aminergic transmitter systems. In: D'Haenen H, Den Boer JA, Westenberg H, Willner P, eds. *Textbook of Biological Psychiatry*. John Wiley & Sons; 2002:895–914.
47. DeYoung CG. The neuromodulator of exploration: a unifying theory of the role of dopamine in personality. *Front Hum Neurosci*. 2013;7:762.
48. Jessup RK, O'Doherty JP. Distinguishing informational from value-related encoding of rewarding and punishing outcomes in the human brain. *Eur J Neurosci*. June 2014;39(11):2014–2026.
49. Delgado MR. Reward-related responses in the human striatum. *Ann N Y Acad Sci*. May 2007;1104:70–88.
50. De Silva A, Salem V, Matthews PM, Dhillo WS. The use of functional MRI to study appetite control in the CNS. *Exp Diabet Res*. 2012;2012:A764017.
51. Bishop SJ. Trait anxiety and impoverished prefrontal control of attention. *Nat Neurosci*. 2009;12(1):92–98.
52. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. *Cell Metab*. May 2008;7(5):400–409.
53. O'Doherty JP. Neural mechanisms underlying reward and punishment learning in the human brain: insights from fMRI. In: Vartanian O, Mandel DR, eds. *Neuroscience of Decision Making*. New York: Psychology Press; 2011:173–198.
54. Botvinick M. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Behav Neurosci*. 2007;7(4):356–366.
55. Sescousse G, Redoute J, Dreher J-C. The architecture of reward value coding in the human orbitofrontal cortex. *J Neurosci*. September 29, 2010;30(39):13095–13104.
56. Mobbs D, Petrovic P, Marchant JL, et al. When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science*. 2007;317:1079–1083.
57. Mobbs D, Marchant JL, Hassabis D, et al. From threat to fear: the neural organization of defensive fear systems in humans. *J Neurosci*. September 30, 2009;29(39):12236–12243.
58. Marschner A, Kalisch R, Vervliet B, Vansteenwegen D, Buchel C. Dissociable roles for the hippocampus and the amygdala in human cued versus context fear conditioning. *J Neurosci*. September 2008; 28(36):9030–9036.

59. Alvarez RP, Biggs A, Chen G, Pine DS, Grillon C. Contextual fear conditioning in humans: cortical-hippocampal and amygdala contributions. *J Neurosci*. June 2008;28(24):6211–6219.
60. Pichon S, de Gelder B, Grèzes J. Threat prompts defensive brain responses independently of attentional control. *Cereb Cortex*. February 1, 2012;22(2):274–285.
61. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Rev Neurosci*. 2011;12:154–167.
62. Wise RG, Lujan BJ, Schweinhardt P, Peskett GD, Rogers R, Tracey I. The anxiolytic effects of midazolam during anticipation to pain revealed using fMRI. *Magn Reson Imaging*. July 2007;25(6):801–810.
63. Yu R, Mobbs D, Seymour B, Rowe JB, Calder AJ. The neural signature of escalating frustration in humans. *Cortex*. May 2014; 54:165–178.
64. Vickery TJ, Chun MM, Lee D. Ubiquity and specificity of reinforcement signals throughout the human brain. *Neuron*. 2011;72(1):166–177.
65. Bach DR, Guitart-Masip M, Packard PA, et al. Human hippocampus arbitrates approach-avoidance conflict. *Curr Biol*. February 18, 2014;24:541–547.
66. Borgwardt SJ, Allen P, Bhattacharyya S, et al. Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. *Biol Psychiatry*. December 2008;64(11):966–973.
67. Aupperle RL, Tankersley D, Ravindran LN, et al. Pregabalin effects on neural response to emotional faces. *Front Hum Neurosci*. 2012;6. Article 42.
68. McNaughton N, Kocsis B, Hajós M. Elicited hippocampal theta rhythm: a screen for anxiolytic and pro-cognitive drugs through changes in hippocampal function? *Behav Pharmacol*. 2007;18:329–346.
69. Young CK, McNaughton N. Coupling of theta oscillations between anterior and posterior midline cortex and with the hippocampus in freely behaving rats. *Cereb Cortex*. January 1, 2009;19(1):24–40.
70. Neo PSH. *Theta Activations Associated with Goal-conflict Processing: Evidence for the Revised Behavioural Inhibition System* [Ph.D. thesis]. Dunedin: Department of Psychology, University of Otago; 2008.
71. Neo PSH, McNaughton N. Frontal theta power linked to neuroticism and avoidance. *Cogn Affect Behav Neurosci*. 2011;11:396–403.
72. Aron AR, Poldrack RA. Cortical and subcortical contributions to stop signal response inhibition: role of subthalamic nucleus. *J Neurosci*. 2006;26:2424–2433.
73. Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci*. 2003;6:115–116.
74. Aron AR. The neural basis of inhibition in cognitive control. *Neuroscientist*. 2007;13:214–228.
75. Floden D, Stuss DT. Inhibitory control is slowed in patients with right superior medial frontal damage. *J Cogn Neurosci*. 2006;18:1843–1849.
76. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction-time responses–a model and a method. *J Exp Psychol Hum Percept Perform*. 1984;10(2):276–291.
77. Neo PSH, Thurlow J, McNaughton N. Stopping, goal-conflict, trait anxiety and frontal rhythmic power in the stop-signal task. *Cogn Affect Behav Neurosci*. 2011;11:485–493.
78. McNaughton N, Swart C, Neo PSH, Bates V, Glue P. Anti-anxiety drugs reduce conflict-specific "theta" – a possible human anxiety-specific biomarker. *J Affect Disord*. 2013;148:104–111.
79. Nieuwenhuys R. The insular cortex: a review. *Prog Brain Res*. 2012;195:123–163.
80. Liang X, Zou Q, He Y, Yang Y. Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. *Proc Natl Acad Sci USA*. January 14, 2013;110(5):1929–1934.
81. Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. *Neuroimage*. March 1, 2011;55(1):8–23.
82. Augustine JR. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res Rev*. October 1996;22(3):229–244.
83. Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Func*. June 2010;214(5–6):519–534.
84. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev*. 2011;35(5):1219–1236.
85. Stoléru S, Fonteille V, Cornélis C, Joyal CC, Moulier V. Functional neuroimaging studies of sexual arousal and orgasm in healthy men and women: a review and meta-analysis. *Neurosci Biobehav Rev*. 2012;36(6):1481–1509.
86. Carlson JM, Greenberg T, Rubin D, Mujica-Parodi LR. Feeling anxious: anticipatory amygdalo-insular response predicts the feeling of anxious anticipation. *Soc Cog Affect Neurosci*. January 2011;6(1):74–81.
87. Mohr PNC, Biele G, Heekeren HR. Neural processing of risk. *J Neurosci*. May 12, 2010;30(19):6613–6619.
88. Rudorf S, Preuschoff K, Weber B. Neural correlates of anticipation risk reflect risk preferences. *J Neurosci*. November 21, 2012;32(47):16683–16692.
89. Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cereb Cortex*. March 1, 2013;23(3):739–749.
90. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. *Brain Struct Func*. June 1, 2010;214(5–6):655–667.
91. Paulus MP, Stein MB. An insular view of anxiety. *Biol Psychiatry*. August 15, 2006;60(4):383–387.
92. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. *Trends Cogn Sci*. April 2014;18(4):177–185.
93. Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. *Neuroimage*. 2003;20:351–358.
94. Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature*. November 11, 1999;402(6758):179–181.
95. Geuze E, van Berckel BNM, Lammertsma AA, et al. Reduced GABAA benzodiazepine receptor binding in veterans with post-traumatic stress disorder. *Mol Psychiatry*. July 31, 2007 online;13(1):74–83.
96. Moller M, Jakobsen S, Gjedde A. Parametric and regional maps of free serotonin 5HT1A receptor sites in human brain as function of age in healthy humans. *Neuropsychopharmacology*. August 2007;32(8):1707–1714.
97. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol Psychiatry*. September 1, 2003;54(5):504–514.
98. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biol Psychiatry*. September 1, 2003;54(5):515–528.
99. Corr PJ, DeYoung CG, McNaughton N. Motivation and personality: a neuropsychological perspective. *Soc Pers Psych Compass*. 2013;7:158–175.
100. Richard FD, Bond Jr CF, Stokes-Zoota JJ. One hundred years of social psychology quantitatively described. *Rev Gen Psych*. 2003;7:331–363.

101. Hemphill JF. Interpreting the magnitudes of correlation coefficients. *Am Psychol*. 2003;58:78–80.
102. Carp J. The secret lives of experiments: methods reporting in the fMRI literature. *Neuroimage*. 2012;63:289–300.
103. Holmes AJ, Lee PH, Hollinshead MO, et al. Individual differences in amygdala-medial prefrontal anatomy link negative affect, impaired social functioning, and polygenic depression risk. *J Neurosci*. 2012;32:18087–18100.
104. Kapogiannis D, Sutin A, Davatzikos C, Costa P, Resnick S. The five factors of personality and regional cortical variability in the Baltimore longitudinal study of aging. *Hum Brain Mapp*. 2013;34:2829–2840.
105. Poppe A, Barch D, Carter C, Ragland D, Silverstein S, MacDonald A. Test-retest reliability of GLM and ICA in schizophrenia patients and healthy controls. *Biol Psychiatry*. 2014;75:373S–374S.
106. Connelly BS, Ones DS. An other perspective on personality: meta-analytic integration of observers' accuracy and predictive validity. *Psychol Bull*. 2010;136:1092–1122.
107. Vazire S. Who knows what about a person? The self–other knowledge asymmetry (SOKA) model. *J Pers Soc Psychol*. 2010;98:281–300.
108. Kirby KN. One-year temporal stability of delay-discount rates. *Psychon Bull Rev*. 2009;16:457–462.
109. Ohmura Y, Takahashi T, Kitamura N, Wehr P. Three-month stability of delay and probability discounting measures. *Exp Clin Psychopharm*. 2006;14:318–328.
110. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. *J Pers Soc Psychol*. 1994;67:319–333.
111. Schandry R. Heart beat perception and the emotional experience. *Psychophysiology*. 1981;18:483–488.
112. John OP, Naumann LP, Soto CJ. Paradigm shift to the integrative Big Five trait taxonomy: history: measurement, and conceptual issues. In: John OP, Robins RW, Pervin LA, eds. *Handbook of Personality: Theory and Research*. New York: Guilford Press; 2008:114–158.
113. Markon KE, Krueger RF, Watson D. Delineating the structure of normal and abnormal personality: an integrative hierarchical approach. *J Pers Soc Psychol*. 2005;88:139–157.
114. Saucier G. Recurrent personality dimensions in inclusive lexical studies: indications for a big six structure. *J Pers Soc Psychol*. 2009;77:1577–1614.
115. DeYoung CG. Personality neuroscience and the biology of traits. *Soc Pers Psych Compass*. 2010;4:1165–1180.
116. DeYoung CG. Cybernetic Big Five Theory. *J Res Pers*. 2014;56:33–58.
117. McNaughton N, Corr PJ. Approach, avoidance, and their conflict: the problem of anchoring. *Front Syst Neurosci*. 2014;8.
118. Depue RA, Collins PF. Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation and extraversion. *Behav Brain Sci*. 1999;22:491–569.
119. Quilty LC, DeYoung CG, Oakman JM, Bagby RM. Extraversion and behavioural activation: integrating the components of approach. *J Pers Assess*. 2014;96:87–94.
120. Wacker J, Mueller EM, Hennig J, Stemmler G. How to consistently link extraversion and intelligence to the catechol-o-methyltransferase (COMT) gene: on defining and measuring psychological phenotypes in neurogenetic research. *J Pers Soc Psychol*. 2012;102:427–444.
121. Chavanon ML, Wacker J, Stemmler G. Paradoxical dopaminergic drug effects in extraversion: dose-and time-dependent effects of sulpiride on EEG theta activity. *Front Hum Neurosci*. 2013;7:A117.
122. Depue RA, Luciana M, Arbisi P, Collins P, Leon A. Dopamine and the structure of personality: relation of agonist-induced dopamine activity to positive emotionality. *J Pers Soc Psychol*. 1994;67:485–498.
123. Depue RA, Fu Y. On the nature of extraversion: variation in conditioned contextual activation of dopamine-facilitated affective, cognitive, and motor processes. *Front Hum Neurosci*. 2013;7:A288.
124. Mueller EM, Burgdorf C, Chavanon ML, Schweiger D, Wacker J, Stemmler G. Dopamine modulates frontomedial failure processing of agentic introverts versus extraverts in incentive contexts. *Cogn Affect Behav Neurosci*. June 2014;14(2):756–768.
125. Rammsayer TH. Extraversion and dopamine: individual differences in response to changes in dopaminergic activity as a possible biological basis of extraversion. *Eur Psychol*. 1998;3:37–50.
126. Rammsayer TH, Netter P, Vogel WH. A neurochemical model underlying differences in reaction times between introverts and extraverts. *Pers Individ Differ*. 1993;14:701–712.
127. Wacker J, Stemmler G. Agentic extraversion modulates the cardiovascular effects of the dopamine D2 agonist bromocriptine. *Psychophysiology*. 2006;43:372–381.
128. Wacker J, Chavanon ML, Stemmler G. Investigating the dopaminergic basis of extraversion in humans: a multilevel approach. *J Pers Soc Psychol*. 2006;91:171–187.
129. Wacker J, Mueller EM, Pizzagalli DA, Hennig J, Stemmler G. Dopamine-D2-receptor blockade reverses the association between trait approach motivation and frontal asymmetry in an approach-motivation context. *Psychol Sci*. 2013;24:489–497.
130. Canli T, Sivers H, Whitfield SL, Gotlib IH, Gabrieli JDE. Amygdala response to happy faces as a function of extraversion. *Science*. 2002;296(5576):2191.
131. Canli T, Zhao Z, Desmond JE, Kang E, Gross J, Gabrieli JDE. An fMRI study of personality influences on brain reactivity to emotional stimuli. *Behav Neurosci*. 2001;115(1):33.
132. Cohen MX, Young JAT, Baek J-M, Kessler C, Ranganath C. Individual differences in extraversion and dopamine genetics predict neural reward responses. *Cogn Brain Res*. 2005;25(3):851–861.
133. Mobbs D, Hagan CC, Azim E, Menon V, Reiss AL. Personality predicts activity in reward and emotional regions associated with humor. *Proc Natl Acad Sci USA*. 2005;102(45):16502–16506.
134. Cremers H, van Tol MJ, Roelofs K, et al. Extraversion is linked to volume of the orbitofrontal cortex and amygdala. *PLoS One*. 2011;6:e28421.
135. DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR. Testing predictions from personality neuroscience. *Psychol Sci*. June 2010;21(6):820–828.
136. Li Y, Qiao L, Sun J, et al. Gender-specific neuroanatomical basis of behavioral inhibition/approach systems (BIS/BAS) in a large sample of young adults: a voxel-based morphometric investigation. *Behav Brain Res*. November 1, 2014;274:400–408.
137. Omura K, Constable RT, Canli T. Amygdala gray matter concentration is associated with extraversion and neuroticism. *Neuroreport*. 2005;16:1905–1908.
138. Bjørnebekk A, Fjell AM, Walhovd KB, Grydeland H, Torgersen S, Westlye LT. Neuronal correlates of the five factor model (FFM) of human personality: multimodal imaging in a large healthy sample. *Neuroimage*. 2013;65:194–208.
139. Hu X, Erb M, Ackermann H, Martin JA, Grodd W, Reiterer SM. Voxel-based morphometry studies of personality: issue of statistical model specification—effect of nuisance covariates. *Neuroimage*. 2011;54:1994–2005.
140. Liu WY, Weber B, Reuter M, Markett S, Chu WC, Montag C. The Big Five of Personality and structural imaging revisited: a VBM–DARTEL study. *Neuroreport*. 2013;24:375–380.
141. Lewis GJ, Panizzon MS, Eyler L, et al. Heritable influences on amygdala and orbitofrontal cortex contribute to genetic variation in core dimensions of personality. *Neuroimage*. September 28, 2014;103C:309–315.

142. Harmon-Jones E, Gable PA, Peterson CK. The role of asymmetric frontal cortical activity in emotion-related phenomena: a review and update. *Biol Psychol*. 2010;84:451–462.
143. Wacker J, Chavanon ML, Leue A, Stemmler G. Is running away right? The behavioral activation-behavioral inhibition model of anterior asymmetry. *Emotion*. April 2008;8(2):232–249.
144. Wacker J, Chavanon ML, Stemmler G. Resting EEG signatures of agentic extraversion: new results and meta-analytic integration. *J Res Pers*. 2010;44:167–179.
145. Coan JA, Allen JJ, McKnight PE. A capability model of individual differences in frontal EEG asymmetry. *Biol Psychol*. 2006;72: 198–207.
146. Pickering AD. The neuropsychology of impulsive antisocial sensation seeking personality traits: from dopamine to hippocampal function? In: Stelmack RM, ed. *On the Psychobiology of Personality: Essays in Honour of Marvin Zuckerman*. Oxford: Elsevier; 2004:453–457.
147. Smillie LD, Pickering AD, Jackson CJ. The new reinforcement sensitivity theory: implications for personality measurement. *Pers Soc Psychol Rev*. 2006;10:320–325.
148. DeYoung CG. Impulsivity as a personality trait. In: Vohs KD, Baumeister RF, eds. *Handbook of Self-Regulation: Research, Theory, and Applications*. 2nd ed. New York: Guilford Press; 2010:485–502.
149. Buckholtz JW, Treadway MT, Cowan RL, et al. Mesolimbic dopamine reward system hypersensitivity in individuals with psychopathic traits. *Nat Neurosci*. 2010;13:419–421.
150. Buckholtz JW, Treadway MT, Cowan RL, et al. Dopaminergic network differences in human impulsivity. *Science*. 2010;329:532.
151. Forbes EE, Brown SM, Kimak M, Ferrell RE, Manuck SB, Hariri AR. Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Mol Psychiatry*. 2007;14:60–70.
152. Forbes EE, Brown SM, Kimak M, Ferrell RE, Manuck SB, Hariri AR. Genetic variation in components of dopamine neurotransmission impacts ventral striatal reactivity associated with impulsivity. *Mol Psychiatry*. January 2009;14(1):60–70.
153. Lahey BB. Public health significance of neuroticism. *Am Psychol*. 2009;64:241–256.
154. Cloninger CR, Svrakic DM, Przybecky TR. A psychobiological model of temperament and character. *Arch Gen Psychiatry*. 1993;50:975–990.
155. Spielberger CD, Gorusch RL, Lushene R, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory (Form Y)* CA94306. Palo Alto: Consulting Psychologists Press; 1983.
156. DeYoung CG, Quilty LC, Peterson JB. Between facets and domains: ten aspects of the Big Five. *J Pers Soc Psychol*. 2007;93:880–896.
157. Corr PJ, Cooper A. The Reinforcement Sensitivity Theory of Personality Questionnaire (RST-PQ): Development and Validation, submitted.
158. Frokjaer VG, Mortensen EL, Nielsen FÅ, et al. Frontolimbic serotonin 2A receptor binding in healthy subjects is associated with personality risk factors for affective disorder. *Biol Psychiatry*. 2008;63:569–576.
159. Takano A, Arakawa R, Hayashi M, Takahashi H, Ito H, Suhara T. Relationship between neuroticism personality trait and serotonin transporter binding. *Biol Psychiatry*. 2007;62:588–592.
160. Tauscher J, Bagby RM, Javanmard M, Christensen BK, Kasper S, Kapur S. Inverse relationship between serotonin 5-HT_{1A} receptor binding and anxiety: a [^{11}C]WAY-100635 PET investigation in healthy volunteers. *Am J Psychiatry*. 2001;158(8):1326–1328.
161. Hennig J. Personality, serotonin, and noradrenaline. In: Stelmack RM, ed. *On the Psychobiology of Personality: Essays in Honor of Marvin Zuckerman*. New York: Elsevier; 2004:379–395.
162. White TL, Depue RA. Differential association of traits of fear and anxiety with norepinephrine- and dark-induced pupil reactivity. *J Pers Soc Psychol*. 1999;77:863–877.
163. Servaas MN, van der Velde J, Costafreda SG, et al. Neuroticism and the brain: a quantitative meta-analysis of neuroimaging studies investigating emotion processing. *Neurosci Biobehav Rev*. 2013;37:1518–1529.
164. Schuyler BS, Kral TR, Jacquart J, et al. Temporal dynamics of emotional responding: amygdala recovery predicts emotional traits. *Soc Cog Affect Neurosci*. February 2014;9(2):176–181.
165. Hyde LW, Gorka A, Manuck SB, Hariri AR. Perceived social support moderates the link between threat-related amygdala reactivity and trait anxiety. *Neuropsychologia*. March 2011;49(4): 651–656.
166. Mujica-Parodi LR, Korgaonkar M, Ravindranath B, et al. Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. *Hum Brain Mapp*. January 2009;30(1):47–58.
167. Cremers HR, Demenescu LR, Aleman A, et al. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. *Neuroimage*. January 1, 2010;49(1):963–970.
168. Cunningham WA, Arbuckle NL, Jahn A, Mowrer SM, Abduljalil AM. Aspects of neuroticism and the amygdala: chronic tuning from motivational styles. *Neuropsychologia*. 2010;48:3399–3404.
169. Iidaka T, Matsumoto A, Ozaki N, et al. Volume of left amygdala subregion predicted temperamental trait of harm avoidance in female young subjects: a voxel-based morphometry study. *Brain Res*. 2006;1125:85–93.
170. Koelsch S, Skouras S, Jentschke S. Neural correlates of emotional personality: a structural and functional magnetic resonance imaging study. *PLoS One*. 2013;8:e77196.
171. Cherbuin N, Windsor TD, Anstey KJ, Maller JJ, Meslin C, Sachdev PS. Hippocampal volume is positively associated with behavioural inhibition (BIS) in a large community-based sample of mid-life adults: the PATH through life study. *Soc Cog Affect Neurosci*. 2008;3(3):262–269.
172. Fuentes P, Barrós-Loscertales A, Bustamante JC, Rosell P, Costumero V, Ávila C. Individual differences in the Behavioral Inhibition System are associated with orbitofrontal cortex and precuneus gray matter volume. *Cogn Affect Behav Neurosci*. 2012;12:491–498.
173. Taddei M, Tettamanti M, Zanoni A, Cappa S, Battaglia M. Brain white matter organisation in adolescence is related to childhood cerebral responses to facial expressions and harm avoidance. *Neuroimage*. 2012;61:1394–1401.
174. Westlye LT, Bjørnebekk A, Grydeland H, Fjell AM, Walhovd KB. Linking an anxiety-related personality trait to brain white matter microstructure: diffusion tensor imaging and harm avoidance. *Arch Gen Psychiatry*. 2011;68:369–377.
175. Xu J, Potenza MN. White matter integrity and five-factor personality measures in healthy adults. *Neuroimage*. 2012;59: 800–807.
176. Jackson J, Balota DA, Head D. Exploring the relationship between personality and regional brain volume in healthy aging. *Neurobiol Aging*. 2011;32:2162–2171.
177. Knutson B, Momenan R, Rawlings RR, Fong GW, Hommer D. Negative association of neuroticism with brain volume ratio in healthy humans. *Biol Psychiatry*. 2001;50:685–690.
178. Garcia-Banda G, Chellew K, Fornes J, Perez G, Servera M, Evans P. Neuroticism and cortisol: pinning down an expected effect. *Int J Psychophysiol*. 2014;91:132–138.
179. Miller GE, Cohen S, Rabin BS, Skoner DP, Doyle WJ. Personality and tonic cardiovascular, neuroendocrine, and immune parameters. *Brain Behav Immun*. 1999;13:109–123.
180. Nater UM, Hoppmann C, Klumb PL. Neuroticism and conscientiousness are associated with cortisol diurnal profiles in adults—role of positive and negative affect. *Psychoneuroendocrinology*. 2010;35:1573–1577.

181. Polk DE, Cohen S, Doyle WJ, Skoner DP, Kirschbaum C. State and trait affect as predictors of salivary cortisol in healthy adults. *Psychoneuroendocrinology*. 2005;30:261–272.
182. Shackman AJ, McMenamin BW, Maxwell JS, Greischar LL, Davidson RJ. Right dorsolateral prefrontal cortical activity and behavioral inhibition. *Psychol Sci*. 2009;20:1500–1506.
183. Sutton SK, Davidson RJ. Prefrontal brain asymmetry: a biological substrate of the behavioral approach and inhibition systems. *Psychol Sci*. May 1997;8(3):204–210.
184. Morinaga K, Akiyoshi J, Matsushita H, et al. Anticipatory anxiety-induced changes in human lateral prefrontal cortex activity. *Biol Psychol*. 2007;74:34–38.
185. Everhart DE, Demaree HA, Harrison DW. The influence of hostility on electroencephalographic activity and memory functioning during an affective memory task. *Clin Neurophysiol*. 2008;119:134–143.
186. Harmon-Jones E, Allen JJ. Anger and frontal brain activity: EEG asymmetry consistent with approach motivation despite negative affective valence. *J Pers Soc Psychol*. 1998;74:1310–1316.
187. Harmon–Jones E. On the relationship of frontal brain activity and anger: examining the role of attitude toward anger. *Cognit Emotion*. 2004;18:337–361.
188. Hall PJ, Chong W, McNaughton N, Corr PJ. A economic perspective on the reinforcement sensitivity theory of personality. *Pers Individ Differ*. 2011;51:242–247.