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Abstract	We propose a "deep science" approach that can link neural, affective, and motivational levels of analysis. Recent neuroimaging research has linked neural activity to anticipatory affective experience (i.e., in the Nucleus Accumbens or NAcc to positive arousal and in the Anterior Insula or AIns to general or negative arousal). Activity in circuits implicated in anticipatory affect further predicts motivated behavior in diverse scenarios (with NAcc activity predicting approach and AIns activity predicting avoidance). More extended links can now be forged from lower levels of analysis related to neurochemistry (e.g., release of dopamine and norepinephrine in target regions), as well as to higher levels of analysis related to aggregate choice (e.g., increases versus decreases in market demand). Innovation of new methods with matching resolution has enabled the linkage of previously disparate levels of analysis, which may most rapidly yield applications capable of improving health and welfare.	
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Chapter 7
Toward a Deep Science of Affect and Motivation

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Scientists of the mind have long sought to marry their models with mechanism. For instance, the innovators of neural network models of cognitive processing advised that a thorough understanding of something at one level of analysis also requires understanding at adjacent levels of analysis (Rumelhart, McClelland, & PDP Research Group, 1987). Linking levels of analysis represents the core of the "deep science" approach we advocate below. While such an approach is challenging and often represents a road less traveled in research, it may also offer unique advantages. For instance, linking levels of analysis may provide the most direct route from the scientific goals of observation and explanation to those of prediction and control (Watson, 1913).

This review enlists a deep science approach to reconnect affect and motivation by linking them to a neural level of analysis. The first section looks to the past to define components within levels of analysis and propose a framework for linking levels of analysis. The second and third sections describe current evidence linking neural activity to anticipatory affect and motivated behavior. The fourth section highlights future extensions to other levels of analysis and opportunities for exploration.

Past Foundations

Theories about links between affect and motivation are at least as old as the field of experimental psychology, yet their connection remains unclear (Berridge, 2004). Over time, research on affect and motivation has diverged into separate fields of inquiry, and their connections have been lost or forgotten. Reconnecting affect and

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motivation requires both definitions of these concepts as well as a framework for linking them.

Defining Affect Scientific definitions of affect can be traced to the first experimental psychologist, Wilhelm Wundt, who wrote: "In this manifold of feelings…it is nevertheless possible to distinguish certain different chief directions, including certain affective opposites of predominant character" (Wundt, 1897). Underlying the variety of emotional experiences, Wundt proposed dimensions running from positive to negative, aroused to subdued, and strained to relaxed. Remarkably, research over the following century repeatedly supported Wundt's early suspicions. For instance, studies of diverse emotional stimuli, including words used to describe emotional experience, emotional facial expressions, and responses to various sensory stimuli (e.g., sounds, smells, tastes) have consistently revealed that two independent dimensions can account for over half of their covariance. These independent dimensions have been called valence (running from positive to negative) and arousal (running from high to low) (Lang, Bradley, & Cuthbert, 1990; Osgood, Suci, & Tannenbaum, 1957; Russell, 1980).

Affective dimensions of valence and arousal have the potential to modulate sensory input as well as motor output. Subsequent theorists noted that a quarter turn (45° rotation) of the valence and arousal dimensions yielded continua which might descriptively be labeled "positive arousal" and "negative arousal" (Thayer, 1989; Watson & Tellegen, 1985). Functionally, the arousal component of these rotated dimensions should recruit attention and behavior, while the valence component might direct elicited attention or behavior toward or away from stimuli under consideration (Watson, Wiese, Vaidya, & Tellegen, 1999). The rotated dimensions therefore imply that positive arousal and negative arousal might not only sharpen sensory processing of opportunities or threats, but also could prepare relevant approach or avoidance behaviors, respectively. These dimensions might also evoke distinct affective experiences—with positive arousal eliciting feelings like energy, excitement, and confidence but negative arousal eliciting feelings like tension, anxiety, and irritability. Thus, affective dimensions describe covariance in subjective responses across a range of stimuli rather than to an isolated stimulus (e.g., words, faces, smells). Further, the fact that these affective dimensions can be assessed not only with verbal reports, but also with nonverbal expressive behavior (e.g., facial expression) and peripheral physiology (e.g., skin conductance, heart rate) (Lang, Greenwald, & Bradley, 1993) implies that conscious awareness or symbolic representation is not necessary for affect to modulate perception or behavior (Zajonc, 1980).

Beyond valence and arousal, Wundt proposed a third dimension running from tension to release, which was associated with the passage of time. In the context of motivation, tension versus release might represent affective changes that occur before versus after goal attainment (since behavioral approach and avoidance require both arousal and action). Consistent with Wundt's third dimension, we have proposed that "anticipatory affect" involves increases in positive arousal and/or negative arousal, which then primes appetitive or aversive motivational states that facilitate movement toward or away from stimuli (Knutson & Greer, 2008).

The notion that affect occurs not only in response to significant outcomes, but also in anticipation of them, draws upon more recent theories which imply that arousal can influence both optimal (Bechara, Tranel, Damasio, & Damasio, 1996) and suboptimal risky choice (Loewenstein, Weber, Hsee, & Welch, 2001). These theories, however, typically invoke general arousal without also specifying valence, and so do not clarify when arousal should promote approach or avoidance behavior. The Anticipatory Affect Model sharpens these accounts by positing that positive arousal promotes approach, while negative arousal instead promotes avoidance (Knutson & Greer, 2008). Notably, anticipatory affect can be distinguished from "anticipated affect"—which refers to cognitive predictions about how one will feel in the future after an outcome has occurred, rather than how one feels immediately during anticipation of the outcome (Wilson & Gilbert, 2003). Anticipatory affect instead increases before uncertain goal outcomes occur. In this review, we focus on anticipatory affect, as defined by the independent dimensions of positive arousal and negative arousal, to cleanly link affect to motivation (see the third ring from the center of Fig. 7.1).

Defining Motivation Behaviorally, motivation (derived from the Latin "movere," meaning "to move") can simply be defined as an energization or amplification of ongoing activity. Psychological definitions for motivation, however, have ranged from broad to specific (Berridge, 2004). A broad definition might simply distinguish between different levels of motivation, which might correlate with changes in a state of general arousal. Narrower definitions typically refer to drives to fulfill specific

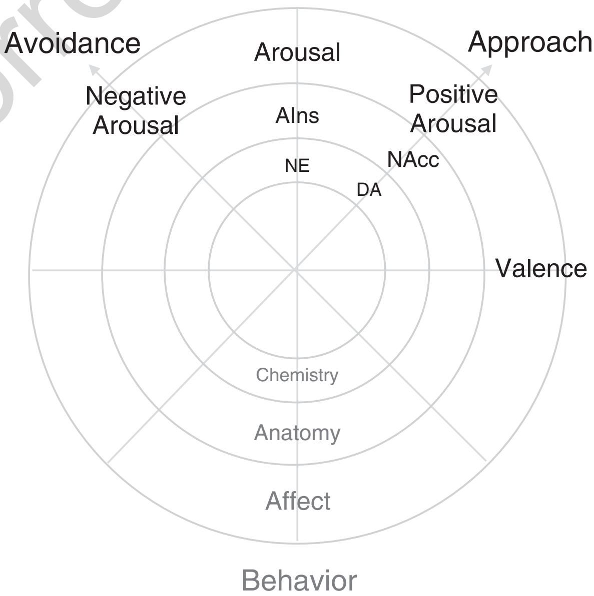

Fig. 7.1 Linking levels of analysis. Concentric circles represent levels of analysis extending from molecular (inner) to molar (outer). These levels depict neurochemistry (*DA* DopAmine, *NE* NorEpinephrine), neuroanatomy (*NAcc* Nucleus Accumbens, *AIns* Anterior Insula), anticipatory affect, and motivated behavior (adapted from Knutson, Katovich, & Suri, 2014)

unmet needs (i.e., which might compensate for a lack of specific necessities like food, water, oxygen, etc.). Between these broad and narrow definitions lies an intermediate definition describing motivations to approach potential opportunities or to avoid possible threats (Craig, 1918). These appetitive and aversive motivations further imply subsequent “consummatory” states capable of terminating motivated behavior after acquisition of an opportunity or avoidance of a threat.

Linking Levels of Analysis At the turn of the twenty-first century, growing computational power and availability of behavioral data (e.g., on the Internet) ushered in a new era of social science—transforming the earlier problem of too little data into a new challenge of too much data. In response, teams of researchers combined efforts to comprehensively map out different levels of analysis—including genetics, epigenetics, metabolics, neural connectivity, and other domains (sometimes applying the “-omics” suffix in the process). A primary goal of these projects typically involved comprehensively mapping all components (“nodes”) and connections (“edges”) within a given level of analysis (e.g., mapping out all the neurons and their connections in a worm; Bargmann, 2012). After a given level of analysis had been thoroughly characterized, researchers assumed that the acquired knowledge could inform research at other levels of analysis. Based on the goal of comprehensively characterizing all components and connections within a given level of analysis, these approaches might collectively be characterized as “broad science” (Knutson, 2016). In contrast to these “broad science” approaches, however, “deep science” approaches might instead seek to first identify critical components in adjacent levels of analysis and then to connect them across levels of analysis (e.g., demonstrating that optogenetic stimulation of midbrain dopamine neurons in rats can increase striatal Functional Magnetic Resonance Imaging (FMRI) activity and approach behavior (Ferenczi et al., 2016)).

Although broad and deep scientific approaches differ in their initial aims, they might serve complementary and synergistic functions. For example, the Research Domain Criteria (RDoC) framework endorsed by the National Institute of Mental Health (Insel et al., 2010) is both horizontally defined by different functional systems, and vertically defined by different levels of analysis (ranging from micro to macro; see Table 7.1). Broad science versus deep science approaches, however, invoke different potential costs and benefits. While broad science approaches require expertise and instrumentation at a single level of analysis, deep science approaches require expertise and instrumentation across two or more levels of analysis. Thus, while broad science approaches might accumulate findings faster within a given level of analysis, deep science approaches might more rapidly link components across levels of analysis.

The deep science goal of linking levels of analysis first requires identifying adjacent levels of analysis and relevant components within them to connect (Cacioppo & Berntson, 1992). A popular three-level scheme proposed by neuroscientist David Marr included: (1) a computational level, describing the goal of a computation; (2) an algorithmic level, describing relevant representations and rules for transforming

Table 7.1 Broad (rows) versus deep (columns) science approaches in the National Institute of Mental Health Research Domain Criteria (adapted from Insel et al., 2010)

	Functional Domains				
Levels of Analysis	*Positive Valence Systems*	*Negative Valence Systems*	*Cognitive Systems*	*Social Process Systems*	*Arousal / Regulatory Systems*
Genes					
Molecules					
Cells					
Circuits					
Behavior					
Self-reports					

them; and (3) an implementational level, describing the machinery supporting the algorithm (Marr, 1982). Though logically and causally connected, Marr noted that these three levels were only "loosely related," allowing some phenomena to be explored at only one level of analysis. He also suggested that many phenomena could be addressed by analyzing higher computational or algorithmic levels before the lower implementational level. Consequently, theorists often interpreted Marr's suggestions in a way that justified focusing exclusively on higher functional levels of analysis (but not lower physical levels), thus pursuing broad but not deep scientific aims.

Although originally applied to visual processing, Marr's scheme might also extend to affective processing—but only after some modifications. First, the three levels could be more transparently relabeled (from bottom to top) as "physiology," "process," and "purpose." This relabeling might reaffirm the implicit aim of using lower-level neurophysiology to constrain higher-level algorithms and computations. Second, the lower level (of physiology) might offer a more promising starting point than the middle (of process) or higher (of purpose) levels of analysis, as causal influences are likely to flow first and fastest up from physiology to process to purpose. Additionally, while the physiological level is necessarily constrained by the design of nature, the purpose level is only constrained by the bounds of human imagination. Third, the ultimate purpose of vision likely differs from that of affect. For instance, meeting the visual computational goal of object identification (originally specified by Marr) might require a series of algorithms capable of identifying features, textures, shapes, objects, and so forth, which are implemented by a "ventral visual" cortical processing stream (DiCarlo, Zoccolan, & Rust, 2012). By contrast, the affective purpose of approaching opportunities while avoiding threats might require processes that weigh potential gains against potential losses, and which are physiologically modulated by ascending monoaminergic projections to critical subcortical targets (Knutson & Greer, 2008).

These overarching differences in purpose imply that linking brain to affect to motivation may ultimately require shifting from an "information processor" metaphor (e.g., in the case of processing visual objects) to a "hedonic sharpener" metaphor (e.g., in the case of processing affect; see Table 7.2). Specifically, the goal of affective circuits is not necessarily to accurately convey information, but rather, to efficiently assess potential gains and losses in order to facilitate rapid action capable of promoting or preserving inclusive fitness. This overarching goal of pursuing positive feelings versus informational accuracy might lead to divergent outcomes over time. But information processing and hedonic sharpening purposes need not necessarily conflict, and might also sequentially and synergistically align.

Once relevant concepts have been identified to connect across levels, evaluating potential links raises a further challenge of measuring relevant concepts at matching resolution. Starting from the physiological level of brain activity, two primary resolution criteria include space (e.g., the size of the brain circuit under consideration) and time (e.g., its speed of operation). For instance, linking monoaminergic activity to anticipatory affect requires consideration of the spatial constraint that neurons carrying these neurotransmitters project to small subcortical regions mere millimeters in diameter, as well as the temporal constraint that the firing of these neurons and subsequent release of neurotransmitters in projection targets varies on a second-to-second basis (Robinson, Venton, Heien, & Wightman, 2003). These constraints imply that neural measures should offer millimeter subcortical spatial resolution as well as second-to-second temporal resolution, while measures of affect should match a similar timescale. Methods that measure concepts with matching resolution could therefore best allow researchers to test new links across levels. Indeed, rapid advances since the turn of the twenty-first century in the discovery of neural mechanisms that drive behavior might have resulted from the rise of neuroimaging methods

Table 7.2 Comparison of levels of analysis for processing visual objects versus anticipatory affect (modified from Marr, 1982)

Vision: "Information Processor"	**Affect**: "Hedonic Sharpener"
Computation: Classify objects	**Purpose**: Approach potential gains while avoiding losses
Algorithm: Identify features, shapes, categories	**Process**: Identify and weigh potential gains against losses
Implementation: Ventral visual cortical stream	**Physiology**: Midbrain monoaminergic projections to subcortical targets

like functional magnetic resonance imaging (FMRI) and neural manipulation methods like optogenetics—which feature overlapping spatial (on the order of millimeters) and temporal (on the order of sub-seconds) resolution (Sejnowski, Churchland, & Movshon, 2014). A deep science approach could therefore not only inform the selection of concepts but also of matching methods capable of linking those concepts across levels of analysis.

Leveling Up from Physiology to Process: Linking FMRI Activity and Anticipatory Affect

Which brain circuits are recruited during the anticipation of good and bad outcomes? Based on the adapted levels of analysis approach described above, one might begin by linking physiology to process. But where in the haystack of the brain should researchers begin to search for the needles of activity that can connect neural activity to anticipatory affect? Over a century of affective neuroscience studies involving animal models could guide the search for relevant neural circuits, while technical developments offer newer methods with matching resolution for linking physiology to process in humans.

Midway through the twentieth century, comparative researchers discovered that electrical and chemical stimulation of specific brain circuits could unconditionally elicit approach or avoidance behavior (Panksepp, 1998). Dramatic examples included "self-stimulation," in which animals would work to increase or decrease electrical or chemical stimulation of their own brain, often to the exclusion of all other incentives—including food, drink, and sex (Olds, 1955; Olds & Milner, 1954). Subsequent research revealed that most circuits that support self-stimulation lie below the neocortex in deeper subcortical or allocortical regions. For instance, electrical stimulation of regions along the ascending trajectory of midbrain dopamine neurons (i.e., projecting from the Ventral Tegmental Area (VTA) to the Lateral Hypothalamus (LH), ventral striatum (including the Nucleus Accumbens, NAcc), and Orbital and Medial Prefrontal Cortex (OFC and MPFC)) can unconditionally elicit approach behavior (Olds & Fobes, 1981). Electrical stimulation of other brain regions (i.e., descending from the Anterior Insula (AIns) and BasoLateral Amygdala (BLAmy) through the Stria Terminalis (ST) to the Medial Hypothalamus (MHyp) and PeriAqueductal Gray (PAG)) can instead unconditionally elicit avoidance behavior (Hess, 1958). Since electrical stimulation of these circuits unconditionally evokes approach or avoidance behavior, they might provide reasonable initial starting points for linking brain activity to anticipatory affect in humans (Knutson & Greer, 2008; Schultz, Dayan, & Montague, 1997).

Linking activity in these circuits to anticipatory affect in humans might next require noninvasive neuroimaging methods capable of resolving activity at millimeter deep spatial resolution and second-to-second temporal resolution. FMRI, developed in the early 1990s, first offered this combination of spatial and temporal resolution (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwong et al., 1992). Early FMRI studies attempted to localize neural activity associated with parametrically varying sensory stimuli (e.g., responses in primary visual cortex to checkerboards flickering at different frequencies) and motor responses (e.g., responses in primary motor cortex to finger tapping at varying tempos; Engel et al., 1994; Rao et al., 1995). Inspired by sensorimotor localization studies, researchers subsequently sought to localize neural activity related to more abstract psychological phenomena, including affect and valuation. While previous research using other neuroimaging methods had explored neural responses to positive and negative emotional stimuli (e.g., standardized sets of affective pictures), many could not control for confounds related to variation in sensory input, motor output, arousal, or expectancy due to limited temporal (e.g., Positron Emission Tomography or PET) or spatial (e.g., ElectroEncephaloGraphy or EEG) resolution.

The spatiotemporal resolution of FMRI allowed researchers to control for some of these confounds by precisely timing the presentation of positive and negative cues and outcomes, and by synchronizing task presentation to image acquisition. Further, although many comparative studies were conducted with primary rewards (e.g., juice) and punishments (e.g., shocks), primary incentives proved difficult to directly compare or scale. Thus, FMRI researchers began to use money as a flexible but controllable incentive that could be inverted, scaled, cued, and delivered to humans (Delgado et al., 2000; Elliott, Friston, & Dolan, 2000; Knutson, Westdorp, Kaiser, & Hommer, 2000; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). For instance, using a Monetary Incentive Delay (or "MID") task, researchers could distinguish neural responses during anticipation of uncertain monetary gains and losses from responses to actual monetary gain and loss outcomes (Knutson, Fong, Adams, Varner, & Hommer, 2001; Knutson, Fong, Bennett, Adams, & Hommer, 2003). Beginning in the early 2000s, these FMRI studies using monetary incentives began to yield robust and replicable results. Specifically, while anticipation of increasing gains proportionally increased activity in the ventral striatal NAcc, dorsal striatal medial caudate, and AIns, anticipation of increasing losses proportionally increased activity only in the medial caudate and AIns (Knutson, Adams, Fong, & Hommer, 2001). Gain outcomes, on the other hand, increased activity in the MPFC and ventral striatal putamen (Delgado et al., 2000), whereas loss outcomes tended to increase activity in the AIns (Knutson et al., 2003).

Initial localization of neural responses during incentive anticipation with event-related FMRI raised further questions about the scope and limits of these findings, which were subsequently addressed by research. First, NAcc activity during anticipation of secondary (or unlearned) monetary gains and AIns activity during anticipation of monetary losses also generalized to anticipation of primary (or unlearned) gustatory gains and losses (e.g., tasting sweet juice vs. salty tea; O'Doherty, Deichmann, Critchley, & Dolan, 2002), suggesting that anticipatory activity does not depend on the sensory modality of outcomes. Second, NAcc activity during anticipation of gains and AIns activity during anticipation of losses did not depend on a subsequent motor response requirement (Ramnani, Elliott, Athwal, & Passingham, 2004). This activity could be augmented by anticipating a motor response, however, particularly in dorsal striatal regions including the medial caudate (Tricomi, Delgado, & Fiez, 2004). Third, NAcc activity during anticipation of gains and AIns activity during anticipation of losses could be elicited by subliminally presented cues, suggesting it does not require conscious awareness (Pessiglione et al., 2008). Fourth, NAcc activity during anticipation of gains could augment other types of subsequent behavior, including memory (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006) and effort (Pessiglione et al., 2007), implying that anticipatory activity has the capacity to modulate a broad range of outputs. Fifth, adding other attributes to cues during anticipation of gains and losses (e.g., probability, delay) tended to increase MPFC activity as well, consistent with the MPFC playing a role in value integration (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005). Together, these findings suggest that neural activity during anticipation of gains and losses is robust, can be elicited by a flexible spectrum of cues, and can potentiate a broad range of responses.

Two decades and hundreds of studies later, these patterns of anticipatory activity have been largely confirmed by several meta-analytic reviews of FMRI studies of incentive processing (Bartra, McGuire, & Kable, 2013; Clithero & Rangel, 2013; Diekhof, Kaps, Falkai, & Gruber, 2012; Knutson & Greer, 2008; Liu, Hairston, Schrier, & Fan, 2011; Sescousse, Caldú, Segura, & Dreher, 2013). Moreover, when self-reported affective responses to incentive cues are probed, the anticipation of monetary gain proportionally increases positive arousal, whereas the anticipation of monetary loss proportionally increases negative arousal (Cooper & Knutson, 2008). Finally, individual differences in NAcc responses to large gain cues correlate with cue-elicited positive (but not negative) arousal, whereas individual differences in medial caudate and AIns responses to large loss cues correlate with cue-elicited negative arousal as well as positive arousal (Samanez-Larkin et al., 2007). Together, these findings suggest that anticipation of gain elicits proportional activity in the NAcc and correlated positive arousal, whereas anticipation of loss elicits proportional activity in the AIns and medial caudate and correlated general arousal—linking brain activity to anticipatory affect (see also: Kruschwitz et al., 2018; Kühn & Gallinat, 2012).

Unexpectedly, this pattern of findings appeared more robustly for anticipated gain than for anticipated loss. Whereas gain anticipation clearly increases NAcc, medial caudate, and AIns activity, loss anticipation also seems to increase medial caudate and AIns activity. So, while NAcc activity aligns well with positive arousal, AIns and medial caudate activity appear to more closely align with general arousal. Despite this apparent absence of a full dissociation, given the relative difference in regions' alignment with valence, researchers should still be able to use activity in the NAcc to infer positive arousal, and relative activity in the AIns versus the NAcc to infer negative arousal (Knutson et al., 2014; Fig. 7.1). Together, these findings could help to resolve a debate about whether NAcc activity correlates with the experience of affective valence or salience (Berridge & Robinson, 1998; Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004) by suggesting that it is associated with both positivity and arousal—and that the experience of anticipatory affect is likely to be fleeting (Cooper & Knutson, 2008; Litt, Plassmann, Shiv, & Rangel, 2011).

Leveling Up from Process to Purpose: Linking Anticipatory Affect and Incentive Motivation

After establishing links from brain activity to anticipatory affect, could additional links extend to motivated behavior? By 2005, researchers began to realize that FMRI methods could not only clarify how sensory input influences brain activity, but could also elucidate whether some of that brain activity predicts motor output. Research accordingly shifted from the scientific goal of explanation to that of prediction. Specifically, researchers began to examine whether activity in circuits associated with anticipatory affect could predict upcoming motivated behavior. According to an Anticipatory Affect Model inspired by localization findings, if risky propositions are framed as choices that require balancing uncertain gains against uncertain losses, NAcc activity should promote approach and risk-seeking, whereas AIns activity should instead promote avoidance and risk-aversion (Knutson & Greer, 2008; see Fig. 7.2). Subsequent studies investigating whether anticipatory affective activity could predict behavior involved diverse scenarios such as gambling, purchasing, and social interaction.

Early prediction studies focused on financial risk-taking. In an initial study of risk-taking in the context of financial investing, increased NAcc activity predicted both optimal and suboptimal risk-seeking choices, whereas increased AIns activity predicted both optimal and suboptimal risk-averse choices (Kuhnen & Knutson, 2005). Other research indicated that activity in these circuits could predict acceptance versus rejection of risky gambles, respectively (Canessa et al., 2013; Hampton

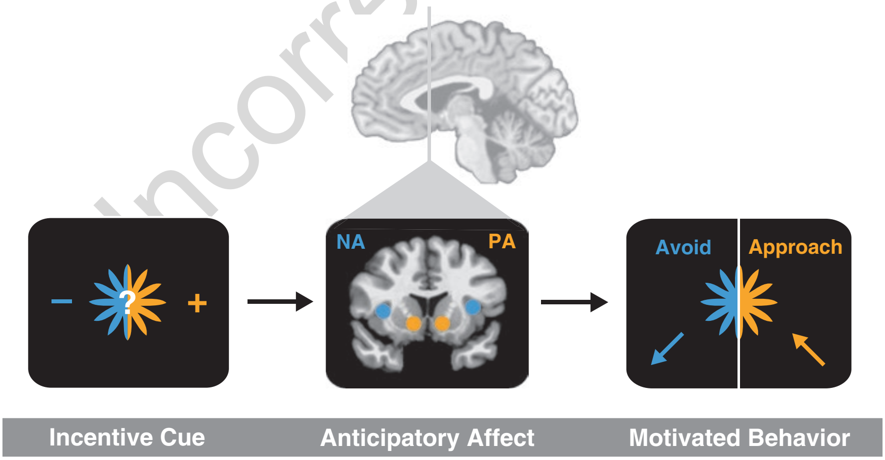

Fig. 7.2 Anticipatory affect model. An incentive cue for an uncertain future outcome initially elicits activity in at least two brain regions (NAcc = orange and AIns = blue), which may correlate with positive arousal and negative arousal, respectively. The balance of activity in these regions then promotes either approach toward or avoidance of the cued outcome (adapted from Knutson & Greer, 2008)

& O'Doherty, 2007; Knutson, Wimmer, Kuhnen, & Winkielman, 2008). Some evidence linked these predictions to affect rather than numerical calculation, since both positive arousal and NAcc activity could account for commonly observed but apparently inconsistent preferences for positively skewed (or lottery-like) gambles, unlike traditional finance theory (e.g., mean-variance accounts; Leong, Pestilli, Wu, Samanez-Larkin, & Knutson, 2016; Wu, Bossaerts, & Knutson, 2011). Further, incidental affective stimuli may alter risky choice by changing activity in these circuits. On the one hand, presenting incidental but attractive pictures before gambles evoked positive arousal and increased risk-taking, an effect partially mediated by increased NAcc activity (Knutson et al., 2008). On the other hand, the threat of shock reduced risk-taking in the case of gambles, partially as a function of increasing AIns activity (Engelmann, Meyer, Fehr, & Ruff, 2015). Further, resting NAcc activity prior to gamble presentation could predict subsequent risk-taking (Huang, Soon, Mullette-Gillman, & Hsieh, 2014). Thus, these findings not only confirm that NAcc and AIns activity increase during risk anticipation (Preuschoff, Quartz, & Bossaerts, 2008), but further demonstrate that activity in these circuits differentially predicts choices to approach or avoid those risks (Wu, Sacchet, & Knutson, 2012), consistent with financial risk analyses that model mean and variance as distinct but oppositely weighted terms (Knutson & Huettel, 2015).

Other prediction studies explored people's choices to purchase consumer products. Early research suggested that increased NAcc activity in response to products and increased MPFC but decreased AIns activity in response to associated prices could predict choices to purchase seconds later (Karmarkar, Shiv, & Knutson, 2015; Knutson et al., 2008; Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007). Subsequent research indicated that brain activity could predict even more distant choices, since mere exposure to products without a choice prompt similarly elicited NAcc and MPFC responses that predicted later choices made outside the scanner (Levy, Lazzaro, Rutledge, & Glimcher, 2011; Smith, Douglas Bernheim, Camerer, & Rangel, 2014). Further, full attention was not necessary, since NAcc, MPFC, and AIns responses to products presented in the context of focused versus distracting tasks equally predicted later choices (Tusche, Bode, & Haynes, 2010). Together, these findings linked anticipatory affect to motivated choice, and further suggested an ongoing implicit influence (Zajonc, 1980). Other studies broadened the range of stimuli under consideration, demonstrating that increased NAcc and MPFC (and sometimes decreased AIns) activity in response to faces, places, pictures, and music could predict subjects' later preferences for those stimuli over other options or money (Lebreton, Jorge, Michel, Thirion, & Pessiglione, 2009; Salimpoor et al., 2013; Smith et al., 2010). Results from another study even suggested that students' NAcc responses to pictures of food and erotica could predict those individuals' weight gain and sexual activity, respectively, several months later (Demos, Heatherton, & Kelley, 2012). Accordingly, reviews of this expanding literature have concluded that NAcc, MPFC, and AIns (negative) responses to varied stimuli can predict later choice behavior (Knutson & Karmarkar, 2014; Levy & Glimcher, 2012).

A third body of research investigated social interaction—often in the context of quantifiable and controllable exchange tasks adapted from Game Theory (Sanfey, 2007). With respect to cooperative behavior, increased NAcc activity predicted increased cooperation with strangers in a Prisoner's Dilemma Game (Rilling et al., 2002), as well as increased reciprocation in a Trust Game (King-Casas et al., 2005). Increased NAcc activity and self-reported positive arousal also predicted choices to give resources to strangers and charities in tasks similar to a Dictator Game (Genevsky, Västfjäll, Slovic, & Knutson, 2013; Harbaugh, Mayr, & Burghart, 2007; Krueger et al., 2007; Park, Blevins, Knutson, & Tsai, 2017). With respect to competitive behavior, however, increased AIns activity in response to unreciprocated cooperation predicted subsequent defection in the Prisoner's Dilemma Game (Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004). Increased AIns activity also predicted rejection of unfair offers, even at personal cost, in the Ultimatum Game (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). Although self-reported affect was not assessed in many of these dynamic interaction studies, several lines of evidence implicated anticipatory affect promoting acceptance or rejection of social offers. For instance, the presence of MPFC lesions is associated with increased rejection of unfair offers in the Ultimatum Game (Koenigs & Tranel, 2007). Further, induction of negative affect also increased rejection of unfair offers in the Ultimatum Game, and this effect was mediated by increased AIns activity (Harlé & Sanfey, 2007). Thus, as summarized in reviews, NAcc activity and positive arousal can foster cooperation, whereas AIns activity and negative arousal may instead promote competition in the context of social interaction (Knutson & Wimmer, 2007; Ruff & Fehr, 2014; Sanfey, 2007).

These collected findings are consistent with the prediction that neural activity associated with anticipatory affect can predict risky choice (Knutson & Greer, 2008). Specifically, when confronting diverse scenarios (e.g., financial risk, consumer products, and social interactions), NAcc activity predicts choices to approach, whereas AIns activity predicts choices to avoid. While activity in these circuits typically changes on a second-to-second basis, presenting incidental but affect-inducing stimuli immediately before choice can perturb ongoing activity in these circuits, which then appears to alter the upcoming choice. Further, activity in these circuits predicts both consistent and inconsistent choices, implying that anticipatory affect contributes to rational as well as irrational choices. Thus, these findings link both brain activity and anticipatory affect to motivated behavior.

Anticipatory affect can be further situated within a comparative anatomical framework that describes frontal and subcortical circuits as connecting in an "ascending spiral" pattern (Haber & Knutson, 2010). This Affect-Integration-Motivation (AIM) framework (Samanez-Larkin & Knutson, 2015) specifies anatomical, chemical, and functional physiology capable of supporting the processing of: (1) anticipatory affect (midbrain dopamine connections to NAcc, midbrain norepinephrine connections to AIns, and glutamatergic connections from AIns to NAcc); (2) value integration (connections of NAcc and AIns indirectly to the MPFC and then back again to the ventral striatum); and (3) incentivized motivation (partially overlapping ascending loops through the dorsal striatum and medial wall of the frontal cortex to the motor cortex). The AIM framework thus presents a componential, sequential, and hierarchical scheme for predicting and testing links from brain activity to anticipatory affect to motivated behavior (Fig. 7.3).

Future Directions

Summary

Remarkable advances since the turn of the twenty-first century have illuminated how brain activity can support anticipatory affect and motivated behavior in humans. These advances likely arose not only from conceptual advances in acknowledging the influence of anticipatory affect in motivating subsequent behavior (Bechara et al., 1996; Finucane, Alhakami, Slovic, & Johnson, 2000; Knutson & Greer, 2008; Loewenstein et al., 2001), but even more from the technical innovation of methods for measuring brain activity immediately prior to behavioral responses.

Rapidly accumulating evidence has begun to link previously disparate levels of analysis (see Fig. 7.1). Initial findings linked brain activity to anticipatory affect, as NAcc activity increases during anticipation of diverse gains (including but not limited to monetary outcomes) and correlates with self-reported positive arousal, but AIns activity increases during anticipation of both losses and gains and correlates with self-reported general or negative arousal. Subsequent findings linked anticipatory affect to motivated behavior, as NAcc activity and positive arousal predict motivated approach toward diverse stimuli (e.g., financial risks, consumer products, social interaction), but AIns activity and negative arousal predict motivated avoidance of those same stimuli.

Together, these links across levels of analysis lay the groundwork for specifying testable causal predictions. On the one hand, dopamine release (and the resulting rate of postsynaptic agonism of D1 receptors) should increase NAcc FMRI activity, positive arousal, and subsequent behavioral approach toward stimuli under consideration (Ferenczi et al., 2016; Knutson & Gibbs, 2007). On the other hand (and more speculatively), norepinephrine release (and the resulting rate of postsynaptic agonism of AD1B receptors) should increase AIns FMRI activity, general or negative arousal, and subsequent behavioral avoidance of stimuli under consideration. The balance of activity in these circuits should predict choices to approach or avoid risky propositions, which feature uncertain gains as well as losses (Knutson et al., 2014; Knutson & Greer, 2008). If both circuits are similarly activated, other neural mechanisms (e.g., descending from the MPFC) may be necessary to resolve differences and thereby facilitate choice (Samanez-Larkin & Knutson, 2015).

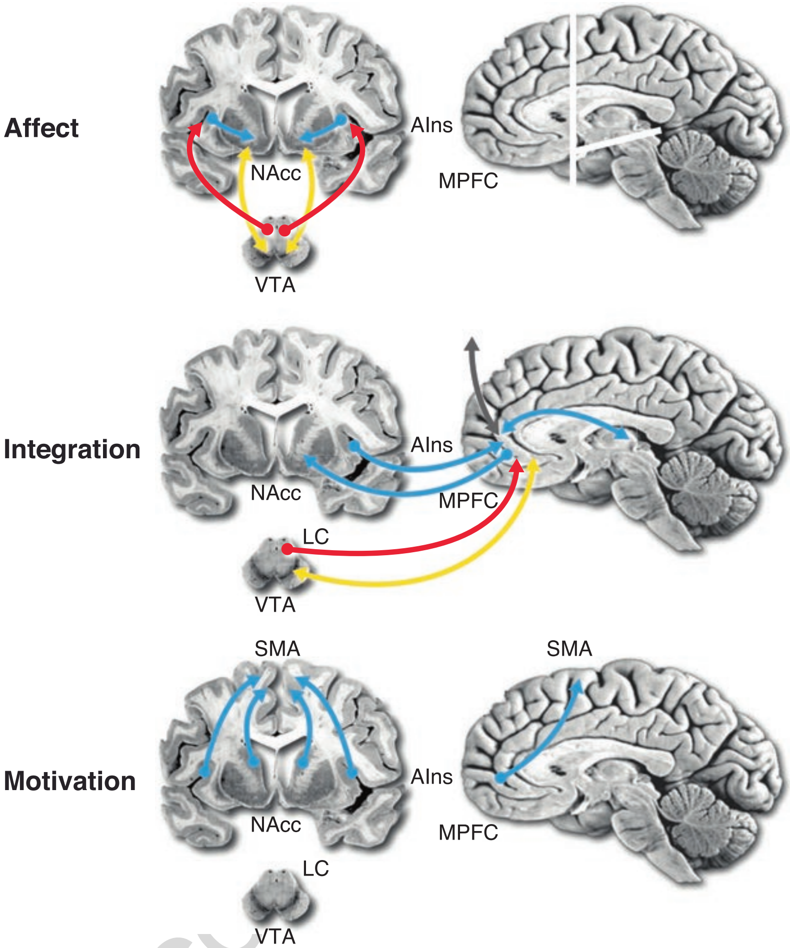

Fig. 7.3 The Affect-Integration-Motivation (AIM) framework. According to the AIM framework, three hierarchical and sequential processes can precede and promote choice. Brain regions involved in these processes are: (top) *Affect* processes associated with: Ventral Tegmental Area (VTA) DopAmine (DA; yellow) neurons projecting to the Nucleus Accumbens (NAcc); Locus Coeruleus (LC) NoradrenalinE (NE; red) neurons projecting to the Anterior Insula (AIns); and AIns glutamatergic (blue) neurons projecting to the NAcc, which potentiate anticipation of gain and loss (white lines on the right indicate the plane of sections depicted on the left); (middle) *Integration* processes associated with: VTA dopamine neurons and LC noradrenaline neurons which also project to the Medial PreFrontal Cortex (MPFC). Additionally, the NAcc indirectly projects to the MPFC via GABAergic connections to the pallidum (not depicted) and glutamatergic projections from the thalamus. The AIns also projects to the MPFC, presumably via glutamatergic connections. Finally, MPFC glutamatergic neurons project directly back to the NAcc (and adjacent VS), facilitating integration of value and other relevant input (for instance, arriving from the medial temporal and lateral frontal cortical regions); (bottom) *Motivation* processes are associated with dorsal striatal and insular glutamatergic neurons that project to the supplementary motor area (SMA), potentiating motor action (adapted from Samanez-Larkin & Knutson, 2015, Nature Reviews Neuroscience)

Implications

A deep science approach need not restrict itself to only three levels of analysis—once links have been established from brain activity to anticipatory affect to motivated behavior, this approach could extend to include additional lower (e.g., neurochemistry) and higher (e.g., group behavior) levels of analysis (see Fig. 7.1).

Leveling Down Links might extend up from an even lower level to connect changes in neurochemistry to FMRI activity in predicted circuits. New comparative methods make causal tests of these links possible. For instance, optogenetic tools now allow researchers to transfect specific neurons with viruses that induce their genetic machinery to express light-sensitive ion channels. These transfected neurons can then be precisely controlled with light via implanted fiber optic probes (Witten et al., 2011). Based on the proposed levels of analysis scheme (see Fig. 7.1), dopamine firing should increase FMRI activity in the ventral striatum, including the NAcc (Knutson & Gibbs, 2007). In fact, research has indicated that in awake rats, phasic optogenetic stimulation of midbrain dopamine neuron firing at a frequency similar to that elicited by reward cues (i.e., 2 s of 20 Hz stimulation) robustly increased FMRI activity in both the ventral and dorsal striatum. Moreover, the magnitude of increased FMRI activity in the ventral striatum (including the NAcc) predicted how intensely rats would work to self-administer that same stimulation (Ferenczi et al., 2016; Fig. 7.4). This robust causal link from optogenetic stimulation of midbrain dopamine neurons to increased striatal FMRI activity has been independently replicated in other laboratories (Decot et al., 2017; Lohani, Poplawsky, Kim, & Moghaddam, 2017). By using tools with matching resolutions, researchers could causally demonstrate that optogenetically stimulating the firing of midbrain dopamine neurons increases NAcc FMRI activity, which further predicts approach behavior. Additional evidence for this link showed that: (1) optogenetically inhibiting midbrain dopamine neuron firing slightly decreased striatal FMRI activity; (2) blocking postsynaptic dopamine receptors blunted this effect; and (3) optogenetically enhancing MPFC input to the striatum also blunted this effect. Together, these findings establish causal links from an even lower level by demonstrating that selective optogenetic stimulation of midbrain dopamine firing can increase NAcc FMRI activity and associated approach behavior. Future research might explore the effects of norepinephrine firing in the AIns in a similar manner.

Leveling Up Links could further extend to an even higher level to connect individual behavior to aggregate behavior. Data from the motivated behavior level might be used to forecast aggregate choice. In the case of "neuroforecasting," researchers have used brain activity in smaller scanned groups to forecast the choices of other larger groups of people outside the laboratory (e.g., in markets on the internet; Knutson & Genevsky, 2018). Growing evidence suggests that sampled FMRI activity can forecast market demand for a diverse array of online products. Specifically, sampled NAcc activity has been used to forecast music sales (Berns & Moore, 2012), the impact of advertisements (Venkatraman et al., 2015), purchases of food

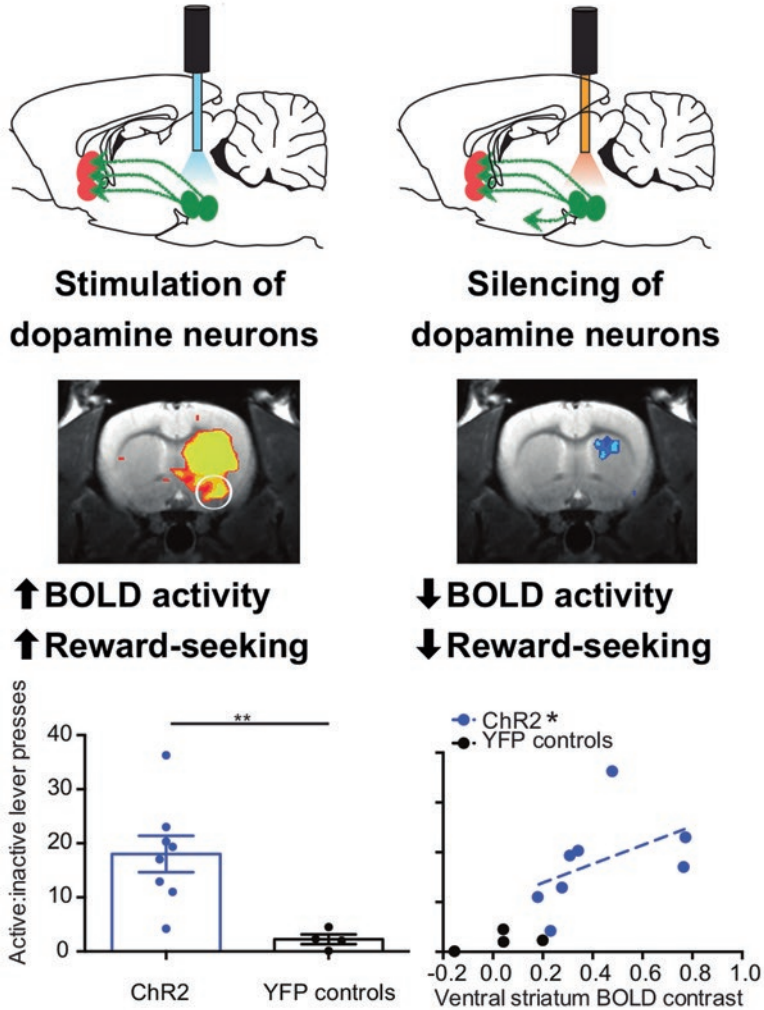

Fig. 7.4 Linking midbrain dopamine neuron firing to NAcc FMRI activity. Optogenetic stimulation of midbrain dopamine neurons increases striatal FMRI activity (top left; white circle indicates ventral striatum), whereas optogenetic silencing of these neurons mildly diminishes striatal FMRI activity (top right). Only transfected rats work to self-administer optogenetic midbrain dopamine stimulation (bottom left); and rats with increased ventral striatal activity from optogenetic midbrain dopamine neuron stimulation also work more intensely to self-administer that stimulation (bottom right) (adapted from Ferenczi et al., 2016)

(Kühn, Strelow, & Gallinat, 2016), the spread of news stories on social media platforms (Scholz et al., 2017), and the success of microlending appeals (Genevsky & Knutson, 2015) as well as crowdfunding appeals (Genevsky, Yoon, & Knutson, 2017). Researchers have additionally used group MPFC activity to forecast aggregate responses to smoking cessation appeals (Falk, Berkman, & Lieberman, 2012) and news articles (Scholz et al., 2017). Remarkably, in some cases, neural activity can forecast market behavior even when individual self-report and behavior cannot—potentially supporting a "partial scaling" account in which neural activity in circuits associated with anticipatory affect affords better forecasts than activity in other circuits or even behavioral choice itself (Knutson & Genevsky, 2018). Together, these findings suggest that sampled neural activity can forecast aggregate choice. Further, in some cases, neural measures might augment or even outperform more traditional behavioral measures.

Leaping Levels The linking levels account implies movement from one level up to the next adjacent level in the same direction. In many cases, however, links bridging more than one level have been established. For instance, much of the research reviewed above links neural activity directly to motivated behavior without assessing intermediate anticipatory affect. While not inconsistent with the spatial logic of predictions implied by the linking levels account, these findings raise the possibility that intermediate measures could be refined either conceptually or technically (e.g., substituting momentary implicit measures of affective experience for retrospective explicit measures) to better match adjacent levels. In a more extreme example from neuroforecasting, sampled brain activity forecasts aggregate choice, even when sampled self-reported affect and choice do not. These findings may imply that some lower-level components can reveal "hidden information" about higher-level components (Ariely & Berns, 2010), and possibly, that concepts at intermediate levels need further refinement (e.g., mixed incentives may induce ambivalent affective responses). Thus, linking components across levels of analysis may provide clues for future conceptual and technical refinement of relevant measures.

Recursive Influence Unlike functional accounts that start from higher levels of analysis, the current approach builds from lower levels of analysis. Regardless of initial priorities, however, causality likely flows down as well as up the levels of analysis—but not in the same manner. Specifically, downward links might involve distinct processes which operate at longer timescales. For instance, approach behavior only requires neural firing to change on a second-to-second timescale (i.e., dopamine agonism of the postsynaptic receptor opens ion channels which change the membrane potential of the postsynaptic neuron, causing it to fire). Reward learning, however, requires genetic transcription to modify neural membranes and alter receptor expression, which necessarily unfolds over a longer timescale on the order of hours (Hyman, Malenka, & Nestler, 2006). Thus, reward learning might reciprocally influence reward anticipation, but only at this longer timescale after upward and downward causal influences have cycled through the system. By implication, then, tracking recursive causation from higher to lower levels might require distinct methods featuring different spatial and temporal resolutions. Studying reciprocal links across levels of analysis (both upwards and downwards) might ultimately enhance scientific understanding of how components at different levels interact over time, both with respect to negative feedback mechanisms typical of homeostatic regulation (e.g., the cycle of food appetite, consumption, and satiety), as well as positive feedback loops that sometimes arise in the context of pathological dysregulation (e.g., escalating addiction to stimulants).

Limits

The deep science approach prioritizes depth over breadth, and so has associated costs as well as benefits. Critically, researchers need to first identify and extend from sparse nodes that can support robust, reliable, and ideally causal links across levels. This might come at the cost of conceptual richness associated with characterizing all the connections within a single level of analysis. The initial sparsity of the deep science approach, however, hopefully leaves gaps open for more extensive exploration later.

Emotion Emotion is notably absent from the levels of analysis framework presented so far. While Wundt believed that neural mechanisms drove both affect and emotion, he also stated that affective qualities infused all emotions but that emotions also required a higher and more complex level of description. He did not, however, specify exactly how affect might link to emotion (Wundt, 1897). Following these historical claims and more recent arguments (Russell & Barrett, 1999), we also suspect that broad dimensions of affect underpin more specific categorical emotions. One intriguing possibility is that different movements through affective space (or "affect dynamics") might imply more categorical emotional states (Kirkland & Cunningham, 2012; Nielsen, Knutson, & Carstensen, 2008). While elegant measures of affect dynamics have been used to describe changes in experience at longer timescales of hours or days (Kuppens, 2015; Kuppens, Oravecz, & Tuerlinckx, 2010), a challenging but tantalizing line of future research might attempt to map affect dynamics at the more rapid timescale of seconds—which might most closely match the neural and affective measures described above (Knutson et al., 2014).

Connecting affect dynamics to emotion at matching temporal resolution might in turn demonstrate that affective qualities and their dynamics underlie different categorical emotions. For instance, starting from an affective baseline state, movement up and to the right might imply excitement, to the right happiness, down and to the right calmness, down and to the left sadness, to the left anger, and up and to the left anxiety (all predictions which would require verification with empirical data). Linking neural and affective levels of analysis might provide a framework for charting out these affect dynamics, which could be tested for specific mapping to temporally precise probes of emotional experience (see also Kirkland & Cunningham, 2011). Further avenues for exploration might include individual differences in affect dynamics and their relationship to emotional traits as well as psychiatric symptom profiles (Davidson, 2015). If affect dynamic probes can yield reliable and valid results, they might be used to assess the impact of various interventions (ranging from psychological to pharmacological). Thus, affect dynamic probes might eventually improve the accuracy of diagnoses as well as the tracking of changes in psychiatric symptoms.

Self-Awareness Some theorists have asserted that affective experience requires self-aware reflection, and possibly verbal representation (e.g., Barrett, Mesquita, Ochsner, & Gross, 2007; LeDoux, 2012). Based on the lack of a strong association between brain activity and self-reported emotional experience in earlier neuroimaging studies, these theorists have argued that subcortical neural circuits implicated in anticipatory affect cannot generate emotional experience in humans. The proposition that affective experience requires self-reflective awareness is interesting because studies of lesioned patients (e.g., Stuss, Gow, & Hetherington, 1992) as well as neuroimaging research on healthy individuals (e.g., Northoff et al., 2006) have implicated the prefrontal cortex in self-reflective awareness. Current evidence linking brain activity to affective experience, however, contradicts these assertions by demonstrating that when measures with matching resolution are employed, subcortical brain activity can correlate with self-reported affective experience (i.e., NAcc activity with positive arousal, and AIns activity with general arousal; Knutson & Greer, 2008). Associations of subcortical activity with self-reported affect, however, are often fragile and not large. Future research might profitably explore where, when, and in whom neural activity most robustly correlates with affective experience. Assuming the use of measures with matching resolution, one surprising implication of the linking levels approach is that when brain activity and self-report fail to converge, brain activity may provide a better index of affective experience and associated behavioral tendencies than does self-reported experience. For instance, in stimulant users, NAcc responses to drug cues can predict relapse months later, even when self-reported affect cannot (MacNiven et al., 2018).

Contributions

Philosophical Tractability Demonstrations of causal influence across levels of analysis can refute at least two contrasting views of mental function. The first view, dualism, presumes that body (or brain) and mind exist on separate and mostly unconnected levels of analysis (e.g., Descartes, 1641). Demonstrating that perturbation of neural activity can alter affective experience or motivated behavior suggests that although components exist at different levels of analysis and can be measured separately, components at one level are connected to and can causally influence components at another level. The second view, reductionism (Nagel, 2007), implies that all higher levels of analysis can be reduced to lower levels of analysis. The separation of levels with respect to distinct components, temporally resolved sequential responses, and probabilistic causal influence implies that different levels can still be related. The present view further makes room for a type of "expansionism," since components at lower levels can influence those at a higher level, but likely in combination with many other components inside and outside of that higher level. Based on a deep science approach, demonstrating a lower-level component's necessity for influencing a higher-level component need not imply sufficiency. In fact, the deep science approach offers an intermediate vision that falls between the extremes of dualism and reductionism, and remains capable of preserving distinctions between levels of analysis while simultaneously tracing causal links that connect them.

Causal Impact The linking levels framework thus implies not only the first two scientific goals of description and explanation, but also the last two scientific goals of prediction and control (Watson, 1913). The surveyed findings that link brain activity to anticipatory affect to motivated behavior over the short span of two decades indicate that researchers have moved beyond description and explanation to prediction. The ability of these findings to not only account for but also to predict choice has partially spurred the birth and growth of new hybrid fields of scientific inquiry (e.g., neuroeconomics, neurofinance, neuromarketing, decision neuroscience, consumer neuroscience, and others). Demonstrating causal links across levels of analysis also implies control (limited by inevitable noise and multicausality). Specifically, manipulating a component at one level should have the causal capacity to alter a linked component at an adjacent but higher level.

New tools developed for precise neural manipulations now make possible identification of these linked components, as well as subsequent tests of control (Namburi, Al-Hasani, Calhoon, Bruchas, & Tye, 2016). For instance, optogenetic manipulations of midbrain dopamine neural firing increase ventral striatal FMRI activity, which elicits approach toward self-administration of the optogenetic stimulus (Ferenczi et al., 2016). Identifying these causal links across levels of analysis can then lead to new predictions and tests of control. For example, recent research has indicated that reward anticipation proportionally induces low frequency electrophysiological activity in the NAcc (i.e., in the delta range), and further, that electrical interference with these signals temporarily halted an animal's approach toward appetizing stimuli (e.g., high-fat food; Wu et al., 2017). Thus, consistent with causal links across levels of analysis, manipulating brain activity necessary for anticipatory affect and associated motivated behavior can change the course of that behavior. Demonstrations of causal influence across levels of analysis could inspire more precisely targeted interventions. These interventions might include "closed loop control"—in which a device detects and then interferes with a predictive neural signature to prevent the onset of a pathological experience or behavior (Grosenick, Marshel, & Deisseroth, 2015).

Metaphorical Reframing The goal of linking levels invites reconsideration not only of lower levels of analysis (e.g., physiology) but also higher levels (e.g., purpose) (Table 7.2). Theorists have often based their metaphors for the mind on its assumed general function. Thus, behaviorists favored a reflex metaphor for the mind based on the ability of reflexes to reliably and rapidly translate input into output, whereas cognitivists favored a computer metaphor for the mind based on the capacity of computers to faithfully process information. Here, we propose an adaptive metaphor for a mind that prioritizes survival and procreation. Such a mind would ideally need to rapidly anticipate, detect, and compare opportunities with threats in order to promote approach or avoidance. A concise phrase that captures these functions, alluded to earlier, is the "hedonic sharpener." In contrast to "computer" or "reflex" metaphors, the overarching goal of a hedonic sharpener is neither accuracy nor consistency, but rather rapid action in the service of maximizing pleasant feelings and minimizing unpleasant ones. These feelings presumably signaled potential increases or decreases in fitness and motivated appropriate behavior in the ancestral past (Panksepp, Knutson, & Burgdorf, 2002). The hedonic sharpener metaphor not only implies novel underlying components (e.g., gain anticipation, loss anticipation, value integration, motivated action), but might also better account for behavior that might appear anomalous or suboptimal in the context of alternative reflex or computer metaphors (e.g., reliance on quick heuristics, overconfidence, confirmation bias, biased assimilation of positive versus negative feedback, etc.). One counterintuitive but testable implication of this metaphorical reframing is that in the case of a reflex or computer, input should be more correlated with output than intermediate processing (since information degrades with processing). In the case of the hedonic sharpener, however, intermediate processing should be more correlated with output than input, since the goal of the system is not to faithfully represent incoming information but rather to transform it in a way that facilitates rapid adaptive action.

Conclusion Instead of a closed system, a deep science approach offers an open framework that can be extended or modified by new findings. Thus, the initial links described here raise more questions than they answer. Still, recent findings have clearly begun to link neural activity, anticipatory affect, and motivated behavior. These advances have been enabled by theoretical recognition of the influence of anticipatory affect on motivated behavior and methodological advances in measuring concepts at matching resolution. Based on the speed and promise of these advances, linking levels of analysis may provide the most direct path from the scientific goals of description and explanation to those of prediction and control. By linking previously disparate levels of analysis, the deep science approach could accelerate the development of effective interventions for enhancing human health and well-being.

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