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Depression: A Decision-Theoretic Analysis

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Abstract

The manifold symptoms of depression are a common and often transient feature of healthy life that are likely to be adaptive in difficult circumstances. It is when these symptoms enter a seemingly self-propelling spiral that the maladaptive features of a disorder emerge. We examine this malignant transformation from the perspective of the computational neuroscience of decision making, investigating how dysfunction of the brain's mechanisms of evaluation might lie at its heart. We start by considering the behavioral implications of pessimistic evaluations of decision variables. We then provide a selective review of work suggesting how such pessimism might arise via specific failures of the mechanisms of evaluation or state estimation. Finally, we analyze ways that miscalibration between the subject and environment may be self-perpetuating. We employ the formal framework of Bayesian decision theory as a foundation for this study, showing how most of the problems arise from one of its broad algorithmic facets, namely model-based reasoning.

Contents

INTRODUCTION..... 2
 BAYESIAN DECISION THEORY..... 3
 States and Priors..... 3
 Utility..... 4
 Actions..... 4
 Valuation..... 5
 DEPRESSED DECISIONS: A COMPUTATIONAL OVERVIEW..... 6
 Expected Utility Rate and Vigor..... 6
 Pessimistic States and Priors..... 7
 Pessimistic Computations..... 10
 Model-Free Evaluation and Learning..... 12
 MAINTENANCE..... 13
 External and Internal Inaction..... 13
 Inhibition..... 14
 Learning..... 14
 Emotion Regulation..... 15
 DISCUSSION..... 15

Major depressive disorder (MDD): clinical definition of depression based on a list of symptoms

Bayesian decision theory (BDT): broad theoretical account of valuation and choice; encompasses reinforcement learning and Bayesian approaches, amongst others

Utility: the subjective value of different outcomes to the organism

Model-based (MB) evaluation: estimation of summed future utility of states or actions based on a model of the world; thought to underlie goal-directed decisions

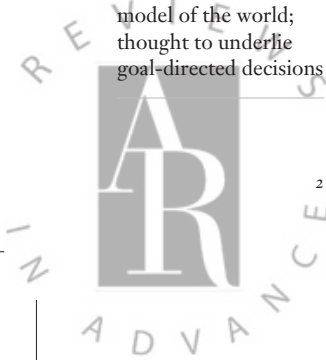
INTRODUCTION

Making appropriate choices in the face of complex, changing, dangerous, and uncertain environments is a high-wire act. It is when falling from such heights that underlying mechanisms are uncovered, revealing in their infelicities something of the finely balanced systems that are responsible. Small missteps expose facets such as the multiple underpinnings of apparently unitary behavior. Vastly larger missteps, as in disease, make manifest more comprehensive failures, arising, for instance, from inherent, mechanistic flaws in the systems involved or from having the systems operate in abnormal regimes.

In major depressive disorder (MDD), failure begins with the eponymous depressed mood, whose symptoms are common, transient, and likely adaptive features of healthy life. In their pathological form, however, the symptoms conspire to impair the affected individual’s ability to lead life and are persistent, failing to be healed by time or changing circumstances. Our central theses are that these symptoms arise from a variety of malfunctions in the evaluation of the likely costs and benefits of circumstances and possible actions and that these aberrant valuations come to be self-reinforcing or compounding.

Underpinning this review is a Bayesian analysis of neural decision making (Dayan & Daw 2008), describing how the expected consequences of different choices in different circumstances should be evaluated to guide behavior toward advantage and away from harm. Bayesian decision theory (BDT) offers a quantitative account of the coupling between evaluation and action, which is a central construct of emotion; BDT also makes ready contact with cognitive, behavioral, and even neural issues and so can capture the multifarious symptoms of mood disorders such as depression

In the section titled Bayesian Decision Theory, we introduce BDT’s framework of valuation. Key components are decision variables such as the long-run utility expected either on average or following particular actions, as well as a spectrum of methods for determining these variables’ values. This spectrum runs from model-based (MB), involving computations such as simulations



of the environment, to model-free (MF), involving learning directly from experienced outcomes. These two extremes have parallels with cognitive and behavioral conceptions of the disorder, respectively. In the next section, we review the features of depression from the perspective of these processes, concluding that the role of MF, compared with MB, reasoning in depression is, perhaps surprisingly, tightly confined. Finally, we consider maintenance of depressed mood as a key differentiator between health and disorder, and we examine why biased evaluations might be self-perpetuating.

Depression is a highly complex disorder to which any short review will fail to do justice. We focus narrowly on the potential computational underpinnings of the symptoms and the way they are maintained; recent authoritative reviews of emotional processing in depression (Mathews & MacLeod 2005, Harmer et al. 2009, Gotlib & Joormann 2010, Elliott et al. 2011, Roiser et al. 2012, Joormann & Vanderlind 2014) should be consulted for many details and ideas. Of particular note, our key issues are not predicated on a categorical definition of depression such as in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association 2013) or the *International Classification of Diseases* (ICD-10) (World Health Organization 1990) and are also not structured around Research Domain Criteria (RDoC) (Insel et al. 2010).

BAYESIAN DECISION THEORY

BDT, which encompasses reinforcement learning, is a comprehensive account of evaluative choice that provides precise links between normative notions in fields such as statistics, economics and ethology; behavioral observations in psychology; and aspects of the neural substrate (Dayan & Daw 2008). Heuristics and approximations are routinely defined in its terms. Furthermore, most pertinently, BDT is increasingly used to organize thinking about the breakdown of choice in psychiatric disorders (e.g., Redish et al. 2008, Maia & Frank 2011, Montague et al. 2012, Huys et al. 2015).

BDT specifies that actions should be chosen that are expected to lead to maximal future utility. Expectations are relative to various forms of uncertainty: stochasticity or (partial) ignorance about the environment and ignorance about the consequences of actions. BDT adopts a Bayesian stance to all uncertainties—calculating expected utilities by weighing different sources of evidence according to the laws of statistical inference.

States and Priors

BDT's first key notion is the state. This has two aspects. First, the objective state of the world comprises everything that actually determines the possible future outcomes the subject will experience dependent on the actions that are taken. This includes transient aspects of the current situation—e.g., in a spatial navigation task, one's current location—but also more global features of how the world works, such as the spatial layout of the maze and the positions of goals. Second, the subjective state is a Bayesian, probabilistic summary of the subject's knowledge of the objective state.

Probabilistic reasoning involves combining current information—to the extent this is not determinative—with knowledge, called the prior distribution, that is either hard-wired or acquired from past experience. The prior plays a pervasive role in a profusion of aspects of evaluation. Priors are sometimes simple; for instance, they may summarize the overall statistics of the quantity of interest, e.g., how often, overall, the subject tends to find herself in each particular state. However, many environments admit richly structured hierarchical descriptions over diverse, interrelated sets of facts. In these cases, prior information can exist at all levels. Priors concerning very general facts

Model-free (MF) evaluation:

estimation of summed future utility of states or actions based on the past experienced utility; thought to underlie habitual decisions

Reinforcement learning:

a formal framework to choose actions that maximize (typically long-term accumulated) returns

States:

in reinforcement learning and BDT, variables that describe or capture all aspects of the environment and agent relevant to the current decision problem



Metareasoning:
decision processes associated with the allocation of (typically limited) computational resources to solve problems

that live at high levels of abstraction, such as the degree to which the environment is controllable (Huys & Dayan 2009), have broad-ranging implications. This is because they affect evaluations of all sorts across the widest possible set of domains that subjects might foresee occupying. Such abstract hyperpriors, potentially many steps removed from observable data, are how we understand in BDT terms the depressive schemas posited in cognitive theories of depression (Beck 1967).

Utility

BDT's second notion is the utility of outcomes or actions. Utility is an assignment of value (reward, punishment, and/or cost) to each different possible outcome or action. Its role in this setting has a couple of special features. First, biological utility is typically assumed to be grounded in fitness. This endows outcomes such as tissue damage, exertion, or ingestion of energy-rich foods with a primary hedonic impact. Second, subjects are considered to make a series of decisions, sequentially encountering outcomes, and obtaining utility at each step. Choices should thus be based on the expected summed future utility over many steps, rather than just the simplification of this to one step.

Psychologists have duly distinguished these more anticipatory quantities that guide behavior (called decision variables) from the primary hedonic impact of rewards or punishments (Berridge & Robinson 1998, Treadway & Zald 2011). We suggest that in depression, there is no simple deficit in primary utility; rather, predictions of long-run future utility are abnormal.

Actions

The final component of BDT concerns the palette of actions that might be attempted and whose qualities need evaluation. This also has some special features: First, subjects must choose the vigor or sloth of actions as well as pick which action to execute. According to formal theories (Niv et al. 2007), the former choice depends on a balance between the actual (e.g., energetic) costs of acting expeditiously and the opportunity cost of not acting quickly, which will postpone actions and rewards to the further future. This opportunity cost is the net utility gained per timestep over the long run; the greater this cost, the greater the value of the opportunities lost by sloth. When the utility rate is estimated to be low, sloth is the optimal result—something we argue underlies a wealth of symptoms in depression.

A second feature concerns the computations involved in BDT. Reasoning about problems requires the allocation of working memory and the judicious use of approximations—these themselves require choices to be made that we call internal actions (Cohen et al. 1996, Dayan 2012). Such actions involve the deployment or control of cognitive and neural mechanisms rather than explicit manipulation of the external environment, but they can be considered as part of a wider conception of BDT. Furthermore, metareasoning about solution methods involves similar assessments as reasoning about solutions (Hay & Russell 2011). We argue that abnormal internal actions bias evaluations in the context of depression.

Finally, Pavlovian (or classical) conditioning (Dickinson 1980) offers a shortcut to control. This involves prespecified actions, including approaching or manipulating food or associated appetitive stimuli and freezing to evade threats. Such hard-wired actions are elicited directly by learned predictions of long-run values and the outcomes that underpin them. The advantage that such actions need not be learned has to be weighed against the disadvantage that they are executed or elicited whether or not they actually achieve their apparently desired goals in terms of gaining rewards or avoiding punishments (Dayan et al. 2006). The latter characteristic has been argued as underpinning various behavioral anomalies.

Valuation

As noted above, the essential task in BDT is to predict the long-run utility that is expected given that an action is performed. This presents a huge computational challenge, even in moderately complex environments. One response to this challenge involves two very broad classes of methods—MB and MF—that are computationally, behaviorally, and neurally somewhat distinct and operate in parallel (Killcross & Coutureau 2003, Daw et al. 2005).

Model-based evaluation. MB evaluation is based on a probabilistic model (\mathcal{M}) of the world, which reports how states may change dependent on the actions that are taken, the outcomes that might thereby arise, and the primary utilities of those outcomes and of the actions themselves. Models encapsulate information that is specific to domains and hence are likely to be represented by a wide variety of neural structures. Most aspects of the models must be learned (with consequences for exploration that we examine below), although some could also be hard-wired.

Models can serve many functions. Of particular relevance here is simulating possible futures—conventionally in what is known as a decision tree—and summing the predicted primary utilities of the outcomes that arise in the simulations to estimate the long-term future value. Indeed, evidence of a phenomenon called preplay in rats (Johnson & Redish 2007, Pfeiffer & Foster 2013) has been interpreted in exactly these terms. Such processes of searching the model are intuitively close to thinking, although MB cognition need not be conscious. Nevertheless, such internal thoughts have real emotional effects—as in mood induction (Coan & Allen 2007), previsualizing an event can have somewhat similar positive or negative affective consequences to experiencing it. As we see below, this central interaction between emotion and cognition provides a framework that integrates decision theory with rumination, emotion regulation (ER), and other features of depression. Unfortunately, decision trees are gargantuan in all but highly restricted environments, and thus actions cannot only be assessed in this way.

Model-free evaluation. MF methods offer a radically different method for evaluating actions. They learn a direct map that takes subjective states and actions as input and predicts long-run utilities. This learning is based on experienced utilities and transitions and occurs via prediction errors, e.g., the difference between the actual utility of an immediate outcome and the expected value for this utility. In the appetitive case, at least, prediction errors appear to be conveyed by the phasic activity of dopamine neurons (Montague et al. 1996). In the form of MF learning associated with such prediction errors, information about long-run utility propagates between states through experienced transitions (Sutton 1988), thus making learning slow and values inflexible to change (because propagation lags experience). However, once learned, retrieving an MF evaluation can be computationally trivial, given a suitable representation of the state. Some components of MF predictions may be hard-wired—for instance, the expected contributions to the long-run utility associated with stimuli that are in view. Rather like Pavlovian actions, these predictions can thereby err if, for example, such stimuli are not in fact attainable.

Combined evaluation. Because MB and MF evaluations have different advantages and disadvantages, it is appealing to combine them so as to realize benefits of each (Daw et al. 2005, Keramati et al. 2011). For instance, synthetic experience generated by simulating states, transitions, and outcomes from the MB system might be used not just for MB evaluation but also to train the MF system (Sutton 1991, Daw et al. 2011, Gershman et al. 2014) and hence transfer knowledge from one to the other.

Decision tree: tree-like structure of possible future outcomes and actions; summing across all branches of a full tree yields long-term return of current actions

Emotion regulation (ER): behavioral or cognitive strategies to alter or guide emotional responses

Prediction errors: these compare expected to actual outcomes and can be used iteratively to improve MF estimates of long-term returns



One prominent potential use for MF evaluation and control may, paradoxically, be metacontrol of the complex processes of MB evaluation. Little convincing evidence for this exists as yet, but it would sever the Gordian knot associated with requiring MB evaluation of metacontrol actions that are themselves regulating MB evaluation of actions.

DEPRESSED DECISIONS: A COMPUTATIONAL OVERVIEW

The prospect of a decision-theoretic view of depression as a disorder of evaluation is that of integrating many of the emotional processing deficits and the behavioral symptoms into a single account. In this section, we examine the extensive experimental work on depression that touches on this perspective. We consider three major themes that emerge: (a) Many of the generic symptoms relate to low expected rates of net utility; (b) low expectations arise from maladaptive priors and the biased construction of internal and external states; and (c) these arise primarily through MB, rather than MF, evaluation.

Expected Utility Rate and Vigor

We noted above that the average rate of the acquisition of utility acts as the opportunity cost of time that should govern energy expenditure and vigor, i.e., how quickly to act. This rate is a global, long-run characteristic of the environment and so is a probable substrate for the longer-lasting emotions that are at issue in depression, such as moods, in contrast to the feelings associated with more transient decision variables, including the expected values of particular actions in particular situations (Eldar & Niv 2015).

As prefigured long ago (Lewinsohn et al. 1979), a low estimated value for this rate could mediate behavioral symptoms of psychomotor retardation and the subjective sense of fatigue or loss of energy, which are central in MDD. Indeed, a compound symptom consisting of both diminished drive and loss of energy is nearly ubiquitous in the disorder (McGlinchey et al. 2006), and diminished drive is among the most discriminatory features defining depression (Mitchell et al. 2009)—outpacing even anhedonia—and is included in ICD-10 as a cardinal symptom of depression.

It is relevant to this interpretation that depression is also a common correlate of various medical conditions, ranging from hematological (e.g., anemia), endocrinological (e.g., hypothyroidism), inflammatory, or immune conditions to cancer (Dantzer et al. 2008). All of these reflect or cause profound alterations in energy utilization and increase the cost of active behavior. The latter reduce the net utility rate and tip the balance of action and opportunity costs toward inaction (Niv et al. 2007). Epidemiological studies frequently report two classes of depression. One is associated with hypersomnia and weight gain (Lamers et al. 2010), both symptoms that could follow from a low estimated utility rate. The other is instead associated with insomnia and weight loss, which is more paradoxical from this perspective. One speculative possibility is that those latter features are more like alternative causes of the depression than symptoms, akin to the other medical causes. Persistent insomnia, for instance, greatly increases the risk of developing depression (Ford & Kamerow 1989) and of experiencing a relapse (Dombrowski et al. 2008), whereas clinical experience shows that iron and thyroid supplementation can treat symptoms of what can appear to be depression.

It has been hypothesized that the level of tonic (rather than phasic) dopamine reports the estimated utility rate (Niv et al. 2007). Indeed, the sloth of voluntary movements and thoughts in Parkinson's disease (PD) is well described by an implicit decision to move slowly (Mazzoni et al. 2007), putatively owing to attenuation in this signal. Furthermore, depression is a very common early sign in PD. However, dopamine's involvement in animal models of depression (Willner

1985, Tye et al. 2013) is better established than in the human condition. The most direct evidence may be hypersensitivity to amphetamines (Tremblay et al. 2002, 2005), consistent with reduced striatal dopamine transporter levels (Savitz & Drevets 2013), putatively as an adaptive consequence of low tonic levels. Importantly, with few exceptions apart from PD, stimulants and dopaminergic stimulation (separate from noradrenergic modulation) are yet to be therapeutically convincing for depression (Candy et al. 2008): Dopaminergic stimulation appears to alter only the short-term expression of symptoms. This suggests that the root cause of MDD is probably separate from, or upstream of, dopamine—possibly resting on pessimistic computations of the estimated utility rate.

Pessimistic States and Priors

The burden thus falls on evaluation, either of the utility rate or of more specific decision variables such as the expected future values of particular actions given a state. The multiple mechanisms of BDT provide diverse potential neurobiological pathways for deleteriously low estimates, stemming from isolated or interacting problems.

Perhaps the most obvious pathological pathway would be a dysfunction of primary hedonic sensitivity. We argue below that the balance of evidence weighs against this account and instead implicates incorrect priors and biased calculations.

Primary utility. If subjects were more sensitive to primary punishments or less sensitive to primary rewards, then the whole basis for evaluation would be biased. We first consider negative aspects. Depressed mood is characteristically dominated by losses, punishments, and aversive stimuli. Patients with depression report more pain symptoms; up to 80% of MDD presentations are associated with complaints of (chronic) pain (Lautenbacher et al. 1994), and pain responses improve with the treatment of depression (López-Solà et al. 2010). Furthermore, chronic pain causes adaptations in the nucleus accumbens that could mediate motivational impairments (Schwartz et al. 2014). However, laboratory-based, controlled measurements tell the rather different story that pain thresholds are by and large increased in depression [with stimulus detection unaffected in relevant modalities, including heat, electric shock, and cold (Buchsbaum 1979; Lautenbacher et al. 1994, 1999)]. That is, patients appear less sensitive to pain.

Abnormally low average net utility could also arise from impairments in the processing of primary rewards. Anhedonia is the second central component of depression (American Psychiatric Association 1994, World Health Organization 1990). It describes a perceived, self-reported inability to enjoy previously pleasurable things, assessed by self-report scales or structured clinical interviews. However, anhedonia correlates only weakly with the standard overall measures of depression severity (Leventhal et al. 2006) and is less diagnostic than depressed mood or reduction in drive or energy (McGlinchey et al. 2006).

Moreover, direct examinations of hedonic responsiveness to primary reinforcers such as sweet solutions have not yielded differences between patients and controls—for instance, MDD patients award similar pleasantness ratings to low sucrose concentrations but higher pleasantness ratings to higher concentrations than controls (Amsterdam et al. 1987; see also Dichter et al. 2010, Berlin et al. 1998, Clepce et al. 2010).

There is thus an inconsistency between individuals' global assessments in self-reports and more systematic measures of both pain and rewards. This pattern hints that the aversive nature of the state of depression is not due to alterations in primary nociception or reward sensitivity.

Secondary utility. The main alternative to deficits in primary utilities is that more elaborative and predictive evaluations associated with richer and distal stimuli are affected. For instance,

depressive status and questionnaire measures of anhedonia do correlate closely with a reduction in the responses to complex rewarding stimuli (Leventhal et al. 2006). Sloan et al. (1997) asked depressed patients and healthy controls to view and rate pictures from the International Affective Picture System (IAPS) database on affective valence and arousal. Patients with depression reported less positive emotion in response to positive images and more arousal to aversive images. The general finding has been replicated with numerous other complex emotional stimuli, from movies to conversations. Furthermore, the findings of blunted affective ratings of positive stimuli extend to a broad set of neurophysiological and behavioral correlates, including negative facial expressions to galvanic skin response, heart rate variability, response bias, and reaction times (see Bylsma et al. 2008 for a meta-analysis).

Several functional magnetic resonance imaging (fMRI) studies have examined the neural correlates of blunted affective responses to complex positive material such as IAPS images, albeit with rather variable results (Elliott et al. 2011). Meta-analyses of these studies (Diener et al. 2012, Zhang et al. 2013) have identified activation in areas such as the caudate, the dorsolateral, and the medial prefrontal cortex, all of which, the problems of reverse inference from fMRI notwithstanding, have been associated with MB reasoning. One interpretation of these activations is, again, that they reflect elaborative, secondary MB evaluations of the stimuli. Indeed, the reinforcer in many of these studies is money, which is unlike other primary rewards (pain, sucrose) whose utility can be immediately experienced. Whence, though, the MB biases?

Priors and the interpretation of state. One main route to biased evaluation is the prior. This can directly influence a wealth of MB and MF processes, ranging from simple biases on the final outcomes of evaluation (Stankevicius et al. 2014) to the underlying nature of the problem being solved. Priors are significant because immediate sensory evidence is generally insufficient to constrain more conceptual or higher-level aspects of the state, e.g., the benign intentions of a person cannot be conclusively inferred from their positive facial expression. In depression, particularly clear biases can be seen in interpreting ambiguous information in terms of unobserved explanations or latent causes. This results in incorrectly pessimistic notions of the state of the subject and her environment.

Cognitive theories of depression have long posited the existence of schemas (Beck 1967) that if activated by sensory experience, trigger automatic negative thoughts. These have been extensively investigated using self-reports such as the dysfunctional attitudes scale (Weissmann & Beck 1978). In terms of BDT, the schemas are best conceptualized as priors at a high level of abstraction (e.g., over possible, unobserved, underlying causes of observations) in a hierarchically structured model of the environment. Biased interpretations of situations (realized as negative automatic thoughts) then result from the (MB) combination of biased priors with evidence that is inconclusive but permissive of negative interpretations (the triggers). These interpretations duly set the stage for biased emotional responses. For instance, when subjects are asked to create a valid sentence from elements of a list of words that allow for either positive or negative solutions (e.g., “winner born I am loser a”), currently and formerly depressed patients choose the negative solutions more frequently and faster than healthy controls (Rude et al. 2003, Cowden Hindash & Amir 2012; see also Lawson et al. 2002).

Biased interpretations of the current state infect all subsequent cognitions and calculations. This is an important means by which even MF evaluations of complex stimuli (as opposed to evaluations of more minimally processed sensations) might appear to be compromised—as these evaluations are of the state as it is assumed to be. According to this view, in the resulting hybrid of MB state inference followed by MF state valuation (Dayan & Daw 2008, Wilson et al. 2014), it is the former, MB, stage that is primarily compromised.

Biased interpretations that arise in helplessness (Maier & Watkins 2005) can be derived from a prior belief that desired outcomes are less reliably achievable (Huys & Dayan 2009). This exerts a negative influence on the predicted values of actions whose consequences are not perfectly known, thus reducing their desirability relative to their costs. As a prior over actions in general, it can have a global influence, affecting many different actions and hence the overall expected reward rate from active behavior as a whole. If applied to internal actions, it can also reduce the expected gains from engaging in MB calculations, possibly impairing concentration and leading to symptoms such as pseudodementia, where even minimal cognitive effort is seemingly avoided.

A further feature associated with priors in BDT is (over)generalization. This is particularly apparent in the invocation of unobserved causes in the hopelessness theory of depression (Abramson et al. 1978), in which poor outcomes are attributed to stable, global failure of the self, whereas positive outcomes are attributed to specific, random events that are not caused by individuals themselves. Hopeless attributions are among the most frequent symptoms both during the prodrome and after recovery from depression (Iacoviello et al. 2010); they strongly increase the risk of developing depression, lead to longer episodes (Cutrona 1983, Alloy et al. 1999), and determine the long-term impact of stressors beyond their emotional impact (Haefel et al. 2007). The issue for generalization is that failure in one domain spreads to other domains via the attribution; indeed, a tendency to overgeneralize can also capture a variety of aspects of animal learned helplessness (Lieder et al. 2013) and possibly some overgeneral aspects of memory observed in depression (Williams et al. 2007).

That prior beliefs in hopelessness and helplessness are part of the subjects' model \mathcal{M} of the world, exerting their influence via MB evaluations, is consistent with many findings. These include animal studies showing that helplessness depends on midline prefrontal areas (Amat et al. 2005) involved in MB reasoning (Killcross & Coutureau 2003, Maier et al. 2006, O'Doherty 2011), findings in humans that the influence of hopeless attributions takes time to crystallize, and evidence that elaboration is an important component of the effects of hopelessness (Haefel 2011).

Attention and the construction of state. Along with this bias in the interpretation of state is a bias in the collection or propagation of information that pertains to the state. We can only afford to process a tiny subset of the flood of sensory information with which we are constantly bombarded. In BDT terms, this subset should be chosen in the light of prior expectations as being most relevant for prevailing choices (Yu et al. 2009, Chikkerur et al. 2010). The resulting allocation of attention is thus a decision-theoretic internal action (Dayan 2012) that can itself be biased. In depression, aversive information can be more likely to attract attention, its processing persists longer, and it is harder to suppress. Analogous biases are seen both in sensory attention and internal processing such as memory. In both cases, this might reflect an expectation that aversive information is more informative (K.E. Williams et al. 1997, Barry et al. 2004).

The capture of attention by emotionally valenced material can be measured by facilitation or interference with other sensory processing, as in the dot probe task. In this, subjects' detection of a dot is speeded if its presentation follows an emotional word presented at the same location (and, conversely, delayed for dots presented at a different location from the word). This effect, which indexes the capture of attention by the emotional stimuli, is enhanced for negative stimuli in depression. In anxiety disorders, negatively valenced or threat-related stimuli attract attention even when presented very briefly (e.g., 14 ms) or masked (Mogg et al. 1993, Mathews & MacLeod 2005). However, in depression, interference is only present if the distracting emotional stimuli are presented for 500 ms or longer. This suggests that there is not a bottom-up, preattentive bias toward negative emotion, but rather, a more elaborative, and hence MB, component is involved. Indeed, depressed patients are no faster at moving toward negative information but do move their

Prior beliefs: beliefs held by the person making the inference prior to observing any evidence

Pruning: cutting off certain branches of a decision tree; in this review, mainly refers to branches that start with a large loss

eyes off it less rapidly (Caseras et al. 2007), spend more time examining it (Kellough et al. 2008, Armstrong & Olatunji 2012), show prolonged amygdala activation to it that persists into unrelated tasks (Siegle et al. 2002), and have a prolonged cortisol response to stress (Burke et al. 2005). This may at least partially account for valence-specific biases in affective go/no-go tasks, too (Erickson et al. 2005).

A related bias, in affective memory, has also been described in depression and is also relevant to the construction of the state (J.M.G. Williams et al. 1997, Watkins et al. 2000, Mathews & MacLeod 2005). For instance, Watkins et al. (2000) asked depressed subjects to encode lists of words during either a perceptually (completing word stems) or a conceptually driven task (generating associated words or definitions). A bias to remember affectively negative rather than positive words emerged, but only in the conceptual condition. This selectivity again suggests that the bias is linked to more elaborative, MB processing.

Pessimistic Computations

Considering the whole decision tree of potential future consequences of an action in MB evaluation is no more possible than considering all the information available from the booming, buzzing confusion of the sensory world. Thus, internal, metareasoning actions of selection are again necessary and are subject to decision-theoretic analyses of their costs and benefits in terms of harvesting more rewards or avoiding more punishments. Computationally costly evaluation efforts should be focused where they are most likely to lead to changes in behavior: Carefully evaluating a course of action that is thought to be suboptimal is only useful if the evaluation might indicate that it is, after all, the best option (Hay & Russell 2011, Keramati et al. 2011).

This has two facets that are significant in depression. First, these metareasoning actions for directing MB evaluation are subject to all the biases discussed above. Second, we have noted that the internal thoughts associated with MB computations have emotional consequences of their own (Coan & Allen 2007) and thus can potentially bias overall evaluations. We interpret this in the setting of ER.

Pruning and internal inhibition. Branches of the decision tree that predict negative utility are typically less promising, suggesting that MB evaluations can safely inhibit (prune) them and implying that the associated trajectories and actions are ignored. Although this strategy reflects rational resource allocation, in healthy subjects, it may contribute to unrealistic optimism (Weinstein 1980)—as avoiding the contemplation of aversive outcomes will lead to undersampling them and thus a positively biased overall valuation (Dayan & Huys 2008). Conversely, a preference in depression for evaluating negative material would necessarily lead to an undersampling of positive material and thereby to an overall negative expectation about the world.

The idea that people inhibit negative paths in MB reasoning was explicitly tested in a sequential planning task (Huys et al. 2012). Although healthy subjects were able to select optimal sequences accurately when no step involved a large loss, they were impaired when the optimal move involved losing a large number of points along the way to an even larger gain. Interpreted as curtailing internal searches through the decision tree upon encountering large losses, pruning correlated with subclinical symptoms of depression. Pruning was suggested to involve serotonin (5-HT) (Dayan & Huys 2008) based on the observation that 5-HT helps mediate behavioral inhibition in response to expected losses (Crockett et al. 2009, Cools et al. 2011). Although this has yet to be confirmed directly, pruning does appear to involve the subgenual and adjacent pregenual anterior cingulate cortices (sgACC and pgACC) (N. Lally, Q.J.M. Huys, N. Eshel, P. Faulkner, P. Dayan & J.P. Roiser, manuscript in preparation). The pgACC mediates the influence of aversive expectations

on choice in primates (Amemori & Graybiel 2012). Both areas are affected by and predictive of treatment response in depression (Mayberg 2009, Fu et al. 2013), and 5-HT modulation targets the sgACC densely.

Pruning is one example of inhibition biasing MB evaluation. In fact, multiple abnormalities in inhibiting the processing of aversive information have been demonstrated in depression that are more general than the attentional biases mentioned above. In negative affective priming tasks, subjects must respond to targets while inhibiting responses to distractors. Never-depressed subjects are slower to respond to a negatively valenced target following suppression of a negatively valenced distractor on the previous trial, suggesting that the inhibition persisted to the next trial. This interference effect is absent in patients with present or past depression (Joormann 2004, 2006). A related effect has been shown using fMRI: Depressed subjects showed weaker dorsolateral prefrontal cortex and stronger amygdala activation to irrelevant negative facial emotions (Fales et al. 2008), suggesting a failure to suppress the processing of the aversive faces. Intrusion of negative affective information is observed when learning word lists (Joormann & Gotlib 2008) and impairs the ability to manipulate negative information in working memory (reordering word lists) (Joormann et al. 2011). Negative information thus appears to hijack processing capacities (Siegle et al. 2002, Gotlib & Joormann 2010) and may underlie some of the more general impairments in task performance in depression (Rock et al. 2014). It is particularly evident in tasks with negative feedback. Probabilistic negative feedback has a larger effect in patients with depression (e.g., Murphy et al. 2003, Taylor Tavares et al. 2008, but see also Remijnse et al. 2009). However, this effect can be so disproportionate as to cause a catastrophic breakdown and a substantial further increase in errors (Elliott et al. 1997, Steffens et al. 2001, Holmes & Pizzagalli 2007, but see also Shah et al. 1997). Thus, the hijacking of processing does not simply lead to more efficient learning from negative information. Rather, it appears to direct processing away from the current task and thereby interfere with it.

Perhaps the most extreme example of the failure of internal inhibition in depression is rumination on aversive events. Rumination, which is usually measured by the self-report ruminative response scale, is a tendency to “focus [repetitively] on the fact that one is depressed; on one’s symptoms of depression; and on the causes, meanings, and consequences of depressive symptoms” (Nolen-Hoeksema 1991, p. 569). It predicts longer and more frequent depression episodes and poorer response to treatment (Nolen-Hoeksema et al. 1993, 2008) and is associated with numerous other poor outcomes. Rumination may in part arise from a failure to inhibit negative cognitions; indeed, several of the behavioral measures of impaired inhibition of negative material (including intrusions on word list learning, interference in affective priming, and persistent amygdala activation) correlate with self-report measures of rumination (Siegle et al. 2002; Joormann 2004, 2006; Ray et al. 2005; Joormann & Gotlib 2008). Hence, failures of inhibiting the processing of aversive information might be seen as a failure of the internal selection mechanisms that normatively ensure limited cognitive resources are adaptively focused. As such, rumination might be a key contributor to producing downwardly biased MB evaluations.

Emotion regulation. Researchers have described ER as a behavioral and cognitive approach individuals use to alter their own emotions. At first sight, this appears to pose a conundrum for BDT: If emotions are subjective counterparts to valuation, then the explicit regulation of emotion would imply an intentional bias in valuation away from the (possibly negative) truth. How could this not be counterproductive when such values are used to guide choice? However, the problem is mitigated by the observation that the imagination of states with positive and negative values that is inherent to MB evaluation leads itself to positive and negative emotions (Coan & Allen 2007). These emotions can be seen as providing guidance to the internal actions associated with



metareasoning, biasing the processes of evaluation toward positive areas, in a manner akin to the inhibition by aversive information considered above (Dayana & Huys 2008, Huys et al. 2012).

Several features of ER tie into evaluation. Antecedent ER strategies (Gross 2002) are said to improve emotions by altering the situation or the interpretation of the emotional material one is exposed to before the emotion itself is experienced. In terms of BDT, this would correspond to an a priori focus on those (aspects of) states that have positive longer-term consequences. As we have seen, interpretation biases can be features of priors, and so negative biases in the priors would naturally reduce positive antecedent ER. A failure in this process could arise in multiple ways from the various errors reviewed so far, implying an MB foundation for the reduced reliance on antecedent ER strategies in depression.

Researchers have observed that depression does not impair the ability to deploy adaptive strategies when they are explicitly instructed; rather, it is the frequency with which patients select these strategies spontaneously when left to themselves that is awry (Ehring et al. 2010, D'Avanzato et al. 2013, Dillon & Pizzagalli 2013, Joormann & Vanderlind 2014). However, this is subtle: People who ruminate typically believe that rumination about the causes of aversive states might bring insight into altering these states (Lyubomirsky & Nolen-Hoeksema 1993). This can hold true, as certain components of rumination, such as a focus on problem solving (Treyner et al. 2003), are adaptive and reduce the length of depressive episodes. However, even if motivated by problem solving, rumination often leads to brooding and passive contemplation of one's negative state, potentially via biases in the aspects of the environment that merit detailed evaluation, and is worsened by failures in the internal adaptive guidance of evaluation, e.g., a lack of pruning. Hence, there could also be a component of failed implementation.

Model-Free Evaluation and Learning

We noted above the paucity of evidence for reflections of depression in alterations to primary utility or to the dopaminergic activity that, by representing prediction errors, is believed to underpin MF learning of rewards. Indeed, evidence of changed MF influences in depression is rather equivocal.

One relevant collection of studies has focused on these prediction errors—based on the distinction between reward outcomes and anticipation. This is expected to be present even in the absence of learning (Forbes et al. 2006, 2009; Knutson et al. 2008; Pizzagalli et al. 2009; Smoski et al. 2009; Robinson et al. 2012). Most such tasks are well known to be strong activators of regions such as the nucleus accumbens and putamen that are thought to be important to MF valuation (albeit not necessarily exclusively; Daw et al. 2011). However, meta-analyses suggested that the blood oxygen–level dependent (BOLD) differences between patients and controls are typically not concentrated on these locations but rather on areas that are more frequently implicated in MB processing (Zhang et al. 2013). Furthermore, only a few studies found correlates with behavioral or self-report measures of anhedonia. The main exception is Forbes et al. (2009), who found that caudate hypoactivity correlated with an experience-sampling measure of daily reported positive affect.

One interpretation is that the differences, such as they are, depend on the sort of elaborative MB processes that were implicated in affecting secondary utilities. This might in turn explain the effect observed in an influential series of studies into a perceptual discrimination task in which monetary rewards were provided asymmetrically for two options (Pizzagalli et al. 2005). The extent to which the bias in the delivery of reward was matched by a learned bias in choice of the options was inversely related to anhedonic symptoms. A computational meta-analysis of many such studies (Huys et al. 2013) suggested that this deficient bias was more closely related to a diminution in the rewarding strength of the monetary outcomes than an impaired ability to accumulate information

across trials (for instance, in constructing MF valuations). Accordingly, it hints again that the problem may rest more on MB evaluation of the rewards than MF learning itself.

Other behavioral studies that have looked at iterative learning emphasize the reduced consequences of rewards but have either not examined (Steele et al. 2007) or not revealed (Chase et al. 2009) a distinction between sensitivity to rewards versus the effect of those rewards on learning—for instance, via an MF prediction error. Meanwhile, fMRI studies of probabilistic learning (Kumar et al. 2008, Remijne et al. 2009, Gradin et al. 2011, Robinson et al. 2012) have identified consistent differences between controls and depressed patients in the nucleus accumbens (believed to be involved in both MF and MB computations; Daw et al. 2011, Huys et al. 2014) but inconsistent differences in midbrain areas consistent with dopaminergic nuclei (which are typically considered to be more MF). The interpretation of these results is further complicated by the lack of behavioral differences between patients and controls in these studies, even though the tasks are sensitive enough to show differences between controls and other patient groups (Gradin et al. 2011, Schlagenhaut et al. 2014).

Overall, studies of iterative learning that should be sensitive to failures of MF valuation have not conclusively identified such dysfunctions, and the structures identified in reward processing have largely been concentrated in areas thought to support MB processing more than MF processing. Hence, the impairments in the motivating value and processing of more complex, nonprimary rewarding stimuli seen in depression may conceivably be due to errors in the construction of the state or in MB valuation.

MAINTENANCE

We have argued that depressed mood is associated with estimates of decision variables such as a low expected average reward. Even in normal, healthy life, opportunities are sometimes scarcer or costs greater, justifying such assessments. Indeed, depression might in part depend on a truly low rate of net utility in the environment (Lewinsohn et al. 1979) as well as misestimates of these same quantities arising from biases in priors, the construction of states, and internal selection for MB evaluation. However, what makes depression such a devastating disease is the persistence of this misevaluation, sometimes in the face of substantial evidence apparently to the contrary. From a BDT perspective, this is a prominent puzzle, as data should ultimately win out and valuations become correct over time. Hence, questions about why initially incorrect evaluations might be self-perpetuating or even self-exacerbating are central.

There could be mechanistic problems with the processes of evaluation. However, all the systems involved are likely to be subject to substantial adaptation (Tobler et al. 2005), homeostatic rebalancing, and cognitive framing (Frederick & Loewenstein 1999, Ariely et al. 2003). These confer substantial robustness to mechanistic deviations (albeit opening up the additional possibility of a flaw in the adaptation point itself, about which there are rather little data).

More pernicious are positive feedback processes. In particular, people are active rather than passive Bayesian observers, choosing which data to observe on the basis of evaluations. Biased evaluations produce biased selections, implying that corrective data may never be observed. Such positive feedback patterns are manifest in several cases, including the control of physical action (exploration and vigor), internal computations (attention, pruning, and ER), and learning. We develop examples in each direction (see Huys et al. 2015 for more details).

External and Internal Inaction

The simplest problem for an active Bayesian observer is sloth. We argued that the vigor and frequency of instrumental action is governed, in part, by expectations about the average reward

(Niv et al. 2007). Either a correct or an incorrect estimation of low average reward will reduce the tendency to act and thereby the rate at which information from the environment is gleaned. For that reason, changes in the environment will be detected later, if ever (Huys 2007). Indeed, sloth may beget ineffective reward-gathering and result in experience that perpetuates the misestimates.

A related example concerns the apparent value of information-gathering actions. This turns on a critical asymmetry between how optimistic and pessimistic beliefs guide choice. Exploration is governed by the expected value of unexplored options and the so-called exploration bonus (measuring how much would be gained if an option that could subsequently be exploited was discovered to be better than the expectation). Pessimistic subjects, i.e., those who rate unknown options poorly and award small exploration bonuses, have a tendency to carry on doing a limited set of actions (or indeed, as discussed above, not doing anything), even if those actions have poor consequences. They thus will not explore to find out true characteristics of the environment and so will remain persistently miscalibrated.

Helplessness can be formalized as a prior directly influencing both of these facets of pessimism. If the world is believed not to be controllable, positive outcomes are assigned to chance, hence reducing the value of unknown options and preventing their exploitation (Huys & Dayan 2009, Huys et al. 2009).

These facts about vigor, exploration, and controllability can equally be applied to internal evaluations, making the cognitive effort of recomputing aberrant MB values appear less worthwhile. Low expectations of their utility also render thoughts relatively more costly, and applying helplessness to expected outcomes of internal evaluations equally flattens them out and thereby reduces their expected value.

Inhibition

Dual to an unwillingness to explore potentially attractive options is an unwillingness to select away negative sensory input, in particular to prune negative parts of the tree in MB evaluation. This would normally be a mechanism for creating what are actually fictitiously optimistic values, but it can seed a positive feedback loop that enforces a positive rather than a negative bias. It can have other effects, too—for instance, inhibiting counterproductive engagement in rumination or worry (Borkovec & Roemer 1995, Wells 1999, Moulds et al. 2007). Conversely, when inhibition in the face of negativity is not effective, these beneficial outcomes are lost. A failure of automatic inhibition could then force goal-directed internal evaluation to focus on the very thing that should be inhibited (Huys 2007).

Given the potential regress of requiring MB evaluation of the internal actions required to compute MB evaluations, MF methods are likely used to estimate the values of MB metareasoning (acknowledging the possible exception implied by the association of pruning with the sgACC. The inhibition inherent in pruning might even be a form of hard-wired Pavlovian response to negativity, not even requiring MF learning, mediated via 5-HT (Cools et al. 2011, Dayan & Huys 2008). This would imply that pharmacologically increasing levels of 5-HT in depression could lead to more efficient pruning. One can imagine why this could be a slow route to remission, as the drugs would have to act against the inertia of the maladaptive positive feedback loop mentioned above.

Learning

Empirical priors bias the present by filling gaps in current information with lessons from past experience. This is particularly clear in learned helplessness, with the unfortunate prior truthfully reflecting previous aversive observations (Maier & Watkins 2005). One might thus hope that future

priors should be amenable to modification through current experience. Some evidence supports this: Being asked to complete ambiguous sentences positively (Tran et al. 2011) or simply being exposed to positive resolutions of ambiguous sentences (Blackwell & Holmes 2010) has shown therapeutic promise, and this improvement appears to be mediated partially through the changes in interpretation biases (Williams et al. 2013)—i.e., adapting the prior. However, the essence of inference using priors is that new experiences, when observed, are integrated with preexisting priors (Bartlett 1932, Xu & Griffiths 2010) rather than being retained in their original form. Prior biases thus lead to biased interpretations being stored, undermining the beneficial effect of corrective experience. This is another example of a self-perpetuating negative proclivity.

Emotion Regulation

Depressed subjects also report a mistrust of positive emotions. The consequent avoidance of these, i.e., a form of blunting, correlates with symptoms of anhedonia (K.E. Williams et al. 1997, Moulds et al. 2007, Liverant et al. 2011, Werner-Seidler et al. 2013). One route to such mistrust is maladaptive priors—as in attribution of outcomes to random events that lie outside the control of individuals themselves. Blunting would reduce learning of the association between the strategy and the emotional outcome. This could help explain the persistence of poor ER choices. There are parallels between this sort of self-perpetuating bias and issues in extinguishing active avoidance—successful performance of avoidance responses implies that subjects never give themselves the chance to observe that the relationship between cue and feared outcome no longer holds. Thus, extinguishing or unlearning maladaptive valuation strategies can be difficult.

DISCUSSION

We have provided a decision-theoretic account of depression. We suggest that key symptoms such as anergia and psychomotor retardation arise from low expected rates of net utility and that depression as an independent disease depends on inappropriately low and self-perpetuating MB evaluations.

Many of the issues leading to negative biases arise through priors or poorly directed forms of selection. These include selection of sensory information from the environment that defines the state (via attention) and selection of information inherent to the metareasoning processes of MB evaluation, such as the failure to prune simulations of potential future states that appear negative.

Little evidence exists for abnormalities in MF evaluation (i.e., the learning of values by incremental accumulation) itself, although MF estimates may be affected in various ways by failures of MB reasoning, especially including state inference. Also, MF processes associated with metareasoning, such as reflexive pruning in the face of negative evaluation, could readily be implicated. Furthermore, although we have argued that little evidence exists for errors in the primary utility function in current studies, which have typically employed DSM criteria to define depression, this is not to say that such errors are either impossible or could not lead to depressive symptoms.

We note that what turns the everyday occurrence of depressed mood into the much more deleterious state of depression has much to do with undue maintenance of the mood. Various positive feedback loops have been implicated, associated, for instance, with active rather than passive observation. How these relatively short-term loops interact with the extremely long relapsing-remitting characteristic of MDD is less clear, and many more interactions are imaginable. However, one key aspect of our account is the multiple paths to these maladaptively maintained low valuations. Indeed, overall, the account paints a somewhat fragile view of valuation as a whole, consistent



with the extremely high lifetime incidence of depression and, indeed, the active debates about the extent to which depression is a unitary condition.

We have not focused on the detailed implications of these notions for treatment. However, the relationship between cognitive and pharmacological routes to therapy bears comment. Cognitive conceptions of depression (Beck 1976) are readily seen in terms of the prior—factors such as persistence, personal responsibility, and generalization (Abramson et al. 1978)—and hence cognitive routes. Pharmacological routes are more obvious approaches in the face of mechanistic flaws. However, the positive feedback loops associated with the maintenance of miscalibration indicate how each can lead to changes in the other. This makes for pressing questions about which aspects would be particularly sensitive to different sorts of treatment.

In this review, we concentrate on computational and algorithmic levels of analysis at the expense of the neural substrate (Marr 1982). We point to some of the evidence (most convincingly from rodents; Killcross & Coutureau 2003) that MB and MF systems are realized in different neural structures. However, recent studies, particularly in human subjects, focus more on the cooperation than the competition between these systems (Daw et al. 2011, Daw & Dayan 2014, Gershman et al. 2014), and there is a woeful dearth of complete process accounts of MB evaluation that would allow us to unpack critical aspects such as the action of priors. In the service of a broad theoretical framework, we have had to take a deliberately partial view of depression, sidestepping many issues around comorbidity, pharmacology, etiology, stress, and even some subtypes such as agitated depression. Filling these details in will require substantial further work, both empirical and theoretical.

Although this review has focused on depression, many of our broad points might be fruitfully applied to anxiety disorders. These are also characterized by aberrant evaluations of stimuli, situations, and actions, albeit concentrated in the aversive domain, with excessive focus on the presence of threats, rather than in the appetitive domain, encompassing the absence or blunting of rewards. The computational neuroscience of threat avoidance is at present less well characterized than that for reward seeking; although much is shared, and indeed there is substantial comorbidity between depression and anxiety disorders, these two functions are not simply mirror images either computationally or psychologically (Boureau & Dayan 2011).

More generally, we should note the rich potential of decision theoretic computational approaches to other psychiatric disorders. They allow diverse approaches to emotion, from learning to attention and ER, to be considered within a unified framework and integrated with other influences arising from varied sources such as internal homeostasis and energy management. Foremost, they provide a foundation based on an understanding of the normal role played by the psychological and neural components that apparently exhibit flaws. This places their aberrance in stark and revealing contrast.

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