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in situ/joie de vivre/laissez-faire/par excellence/per se/raison d'être/vis-à-vis ITALIC: sic

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accompli/ ibid./id./laissez-faire/par excellence/per se/vis-à-vis

ITALIC: c. (circa)/de novo/ex parte/ex post facto/in situ/joie de vivre/passim/raison

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Information Processing in Mood Disorders

Jonathan P. Roiser and Barbara J. Sahakian

Abstract

This article discusses the central role of information processing in mood disorders, distinguishing “cold” (emotion-independent) from “hot” (emotional-dependent) cognition. Impaired cold cognition, which appears in the core diagnostic criteria for both depressive and manic episodes, is a reliable finding in mood disorders. There is good evidence that cold cognitive abnormalities remain in remission, predict poor response to treatment, and are present in unaffected first-degree relatives of patients with mood disorders, suggesting that they are not simply epiphenomena of extreme mood states. Abnormal hot cognition is also a consistent finding in mood disorders. Mood-congruent affective biases and disrupted reward-processing have commonly been reported; the latter is especially relevant for understanding anhedonia. This pattern of disrupted hot and cold cognition is consistent with a cognitive neuropsychological model of depression, which proposes a central role for fundamental information-processing abnormalities in generating symptoms.

Keywords: depression, bipolar, mania, hot cognition, cold cognition, cognition, cognitive, emotional bias, reward, antidepressants

Introduction

Mood disorders are common, distressing, and debilitating conditions that are frequently chronic or recurrent. Common evidence-based treatments include medications, such as selective serotonin reuptake inhibitors (SSRIs) in unipolar depression and lithium in bipolar disorder, and psychological treatments, such as cognitive behavioral therapy (CBT). This chapter argues that abnormal information processing (here referred to simply as “cognitive processing,” or “cognition”) in mood disorders is fundamental to the genesis and treatment of symptoms. The types of relatively basic cognitive processes discussed in this chapter are quite different from the high-level constructs, such as dysfunctional attitudes and faulty reasoning (Beck, 1967; see Chapters 13 and 35 herein), that form the basis of traditional cognitive models of mood disorders and associated

treatment approaches such as CBT. In particular, this chapter considers information processing as assessed by objective neuropsychological or cognitive neuroscience tests, rather than by clinical observation, structured interviews, introspection, or self-report questionnaires. However, rather than being seen as in opposition, these perspectives on cognition in mood disorders should be considered complementary and related to one another: the lower-level processes (bottom-up processing, or “negative perceptions”) may act as building blocks for higher-level constructs (top-down processing, or “negative expectations”), which can themselves act as a scaffold for information processing, in turn influencing lower-level processes.

Why are these basic cognitive processes important in mood disorders? Our theoretical perspective is that what is commonly described and experienced as “mood” is really the summation and interaction of different types of cognitive processes (both lower- and higher-level) (Roiser, Elliott, & Sahakian, 2012). According to this perspective, understanding depression is impossible without understanding the information-processing abnormalities that drive it. This chapter will present evidence that, similar to some high-level cognitive constructs (see Chapter 13), basic cognitive abnormalities both predate and persist beyond mood episodes; that some (but not all) basic cognitive abnormalities are directly influenced by common pharmacological treatments; and that basic cognitive abnormalities may have a partly genetic basis.

Consistent with this emphasis on the importance of information processing in mood disorders, standard diagnostic frameworks such as in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), highlight basic cognitive processes. For example, in the criteria for a major depressive episode: Criterion 8 states that a

depressed individual may have “diminished ability to think or concentrate,” suggesting impaired working memory and attention; while Criterion 2 is *anhedonia*, defined as “markedly diminished interest or pleasure in . . . activities,” implying deficient reward-processing. The criteria for a manic episode include distractibility (Criterion 5), suggesting attentional impairment, as well as elevated goal-directed activity (Criterion 6) and risky behavior (Criterion 7), implying excessive reward-processing. Thus, basic information processing is fundamentally altered in mood disorders, changing patients’ perception of and interaction with the environment, including the social environment. This cognitive impact has a huge influence on their ability to function, whether in the workplace, at school, or at home.

Disrupted cognitive processing in mood disorders also has important treatment implications. Several studies report that marked cognitive impairment predicts poor response to antidepressant medication, independent of baseline symptom severity (Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004), and that cognitive enhancers can aid recovery in both unipolar and bipolar depression (Goss, Kaser, Costafreda, Sahakian, & Fu, 2013). Moreover, certain information-processing abnormalities may prevent severely ill patients from deriving full benefit from psychological treatments, since the latter often require patients to engage in difficult “executive” processes, such as problem-solving and counterfactual thinking. Finally, in some depressed patients, cognitive abnormalities may not resolve completely with treatment, continuing to cause social and occupational impairment even during remission (Hasselbalch, Knorr, & Kessing, 2011). Consistent with such a trait-like feature, cognitive abnormalities have also been reported in first-degree relatives of patients with mood disorders, especially bipolar disorder; hence, they

may be useful in identifying at-risk individuals (Olvet, Burdick, & Cornblatt, 2013) as well as in searching for the neurobiological underpinnings of the disorder. This perspective accords with the National Institute of Mental Health's Research Domain Criteria initiative, which emphasizes the importance of refocusing research into the causes and treatments of mental health problems along neurobiological axes, including objective behavioral measures (Insel et al., 2013).

In this chapter, we distinguish between “hot” and “cold” cognition. “Hot cognition” occurs on tests that have an emotional impact on the individual completing them, either because the stimuli presented are intrinsically emotionally salient (e.g., emotional words, faces, scenes, music), or because feedback on the participant's performance results in an affective state (e.g., satisfaction or disappointment). “Cold cognition” refers to information processing in the absence of any emotional influence. Theoretically, cold cognition is engaged on tests where the stimuli are emotionally neutral, and either feedback is not provided or the outcome of the test is not motivationally relevant (though motivational influences could certainly turn a cold test “hot”; see “Causal Relevance of Cold Cognition in Mood Disorders” below). It is important to note that the distinction between hot and cold cognitive processing is not the same as that between “bottom-up” and “top-down” processing, as both could be either hot or cold. For example, recognition memory for non-emotional objects would be primarily a cold bottom-up process; planning a series of chess moves would engage cold top-down processing; categorization of emotional faces would be primarily a hot bottom-up process; while pessimistic expectations during a high-stakes gambling game would

represent an example of hot top-down processing. Most cognitive tests, whether hot or cold, involve a mixture of bottom-up and top-down processing.

Cold Cognition

Cold Cognitive Impairment Is Common in Mood Disorders

Disrupted cold cognition is a well-established feature of both depression and bipolar disorder. Reliable impairments on pencil-and-paper assessments commonly used to assess function in neurological patients have been observed in depression from the 1970s onwards. Whereas some early studies adopted a classical neuropsychological case-series approach (Cavenar, Maltbie, & Austin, 1979), comparing individual patients against population norms to identify deficits considered to be clinically significant, group case-control designs were more common. By the mid-1990s, numerous comparisons of depressed and non-depressed participants on cognitive measures had been reported, particularly on memory tests.

Burt, Zembar, and Niederehe (1995) performed the first systematic review of this literature, including nearly 100 case-control investigations of memory in depression. This meta-analysis identified deficits in depressed patients in the range of $d = 0.27$ (small) to $d = 0.67$ (medium-to-large), varying across outcome measures (“d” here refers to Cohen’s classic measure of effect size: the standardized difference between group means).

However, several of the constituent studies included participants with organic neurological illness; or they did not match the groups on important demographic variables such as age and educational level, making it difficult to draw firm conclusions.

A later meta-analysis by Veiel (1997), utilizing more stringent inclusion criteria, identified higher effect sizes for memory, in the range of 0.83 to 0.97 (large), and

additionally reported differences in domains of cognitive function other than memory. Performance on tests in the domain “attention and concentration” was, according to Veiel’s analysis, relatively unimpaired in depressed patients (though see below for further discussion of this surprising finding).

Large deficits on cold cognitive measures, especially on tests of memory and executive function, have also been reported in patients with bipolar disorder. These deficits were evident during the euthymic state, as well as during manic or depressive episodes (Bourne et al., 2013; Robinson et al., 2006). The magnitudes of the deficits observed in bipolar disorder are generally larger than those observed in unipolar depression, but smaller than in schizophrenia (Krabbendam, Arts, van Os, & Aleman, 2005). Deficits have typically been found to be greatest during the manic phase. Whereas the known negative impact of mood-stabilizing medication on cognition may be an important confounding factor in studies of bipolar disorder (Roiser et al., 2009; Wingo, Wingo, Harvey, & Baldessarini, 2009), cognitive impairments have also been reported in unmedicated patients and in unaffected relatives of bipolar patients (Olvet et al., 2013), especially in the domains of episodic memory and executive function.

The advent of theoretically based computerized cognitive tests in the 1990s provided an important methodological advance in understanding cognition in mood disorders. One example of this approach is in the use of the Cambridge Neuropsychological Test Automated Battery (CANTAB: see www.cantab.com). Broadly consistent with the results from pencil-and-paper studies, those obtained with the CANTAB provided evidence of impairments on a wide variety of tests in depressed patients, including not only memory and executive function (Elliott et al., 1996), but also

attention (Swainson et al., 2001). (Recall that it was in the domain of attention that Veiel's 1997 meta-analysis yielded a null result.) This pattern was confirmed in a recent meta-analysis of studies using the CANTAB. Moderate- to large-sized deficits were evident on almost all measures assessed (Rock, Roiser, Riedel, & Blackwell, 2014), with similar patterns and degrees of impairment evident in remitted patients as well as in patients tested during a depressive episode. Impairments on CANTAB tests have also been reported consistently in patients with bipolar disorder (Sweeney, Kmiec, & Kupfer, 2000).

The difference in the conclusions of meta-analyses examining attention in depression between paper-and-pencil and computerized tests highlights a key advantage of utilizing computerized assessment. Computerization enables more flexible and temporally precise stimulus presentation than traditional neuropsychological assessments do, as well as more accurate measurement of response times. In the CANTAB, sustained attention is assessed using the Rapid Visual Information Processing (RVIP) test. In the RVIP subjects must, over a several-minute period, detect specific targets presented in a train of hundreds of successively presented stimuli, with interstimulus intervals of under one second. By contrast, because continuous performance paradigms are impractical to administer without a computer, the only measures of "attention" available to Veiel (1997) when he conducted his meta-analysis were variants of the digit-span test from the Wechsler Adult Intelligence Scale. The digit-span test, commonly characterized as a test of maintenance working memory, does not require a high degree of sustained concentration (and in a large meta-analysis of executive function in depression digit-span performance was found to be relatively unimpaired: Snyder, 2013). Therefore, the

apparent discrepancy between the results reported using computerized and pencil-and-paper measures of attention in depression is likely to be due to the fact that different cognitive processes were being assessed.

Causal Relevance of Cold Cognition in Mood Disorders

The precise theoretical significance of cold cognitive impairment in mood disorders is a matter of debate. Some investigators interpret the group differences described above as reflecting a core feature of mood disorders, and probably of central importance in their etiology. Others question the causal relevance of cold cognitive deficits in mood disorders, pointing to the potentially confounding effects of symptoms, especially the motivational deficits that characterize depression (Scheurich et al., 2008). In other words, it is possible that mood disorder patients appear to have impaired cognitive performance because they are distracted by symptoms, because they lack motivation, or because emotional responses on ostensibly cold tasks may interfere with performance (in other words, a “cold” task may be turned “hot”).

Such factors probably do affect measures of cognitive impairment in mood disorders, but they are unlikely to account fully for the observed deficits. Meta-analyses have reported small-to-moderate correlations (r values in the range of 0.11–0.32) between the degree of cognitive impairment and symptom severity (McDermott & Ebmeier, 2009). However, in general, these correlations are insufficient to explain group differences, and might simply reflect the presence of a more severe illness in more cognitively impaired individuals. (See “Clinical Relevance of Cold Cognitive Impairment in Mood Disorders,” below.) In bipolar disorder, impairments are greatest during the manic phase. Importantly, though, cold cognitive deficits have also been reported during

the euthymic phases of unipolar and bipolar depression (Beats, Sahakian, & Levy, 1996; Boeker et al., 2012), suggesting that they are not simply epiphenomena of extreme mood states. It should be noted that there is evidence that ostensibly “cold” tasks may be turned “hot” in depression, such that patients may become discouraged in the face of negative feedback, leading them to exert less effort, or even to give up entirely (which Beats et al., 1996, termed a “catastrophic response to perceived failure”; see also Elliott, Sahakian, Herrod, Robbins, & Paykel, 1997). However, such feedback-related effects are unlikely to provide a complete explanation for abnormal cold processing in depression, since impairments have also been observed on tests that do not feature explicit feedback.

Clinical Relevance of Cold Cognitive Impairment in Mood Disorders

Although standardized cognitive assessments are not often used to aid diagnosis or treatment for patients with mood disorders, cognitive impairment could serve as a useful clinical indicator; for example, predicting severity, the likelihood of responding to treatment, and the risk of future relapse. There is evidence that cognitive impairment is more marked in patients who have a more severe form of illness, such as those whose disorder is more chronic (Hasselbalch, Knorr, Hasselbalch, Gade, & Kessing, 2013), more recurrent (Kessing, 1998; Robinson, & Sahakian, 2008), or characterized by more severe symptomatology during episodes (McDermott & Ebmeier, 2009). Depressed patients who have experienced more episodes also exhibit greater deficits in social and occupational functioning (Coryell et al., 1995), which are related to absenteeism and presenteeism at work (Beddington et al., 2008).

Cold cognitive deficits may also interfere with the effectiveness of treatments for depression. Most of the research on this question has been focused on elderly patients

(reviewed in Pimontel, Culang-Reinlieb, Morimoto, & Sneed, 2012). For example, Story, Potter, Attix, Welsh-Bohmer, and Steffens (2008) reported that more cognitive impairment was associated with less improvement with antidepressant medication in a sample of elderly depressed patients. Deficits in executive function appear to be particularly reliable predictors of poor treatment response in geriatric samples (McLennan & Mathias, 2010). On the basis of such findings, Alexopoulos and colleagues developed a form of psychological therapy specifically tailored to boosting problem-solving in geriatric depression (Alexopoulos, Raue, Kanellopoulos, Mackin, & Arean, 2008), which was found to be more effective than supportive therapy when used as an adjunct to standard antidepressant treatment (Arean et al., 2010). This is consistent with complementary evidence from trials using the cognitive enhancer modafinil as an adjunct to standard pharmacological treatment in younger patients to improve symptomatic response in both unipolar and bipolar depression (Goss et al., 2013). However, as none of the trials addressing this issue have included cognitive assessments, the mechanism driving this effect remains to be clarified. Finally, enhancement of cold cognitive processing is a plausible explanation for the antidepressant effects of novel brain-stimulation therapies, such as transcranial direct current stimulation (tDCS) (Kalu, Sexton, Loo, & Ebmeier, 2012) and repetitive transcranial magnetic stimulation (rTMS) over the prefrontal cortex (George, Taylor, & Short, 2012). For example, one study found that treatment-resistant depressed patients who had improved attentional control after a single rTMS session (when mood effects were not yet apparent) showed the greatest symptomatic improvement following stimulation sessions over the succeeding two-week period (Vanderhasselt, De Raedt, Leyman, & Baeken, 2009).

Hot Cognition

Emotional Biases in Mood Disorders

It is well established that depressed individuals exhibit more negatively biased responses than healthy volunteers on tests of emotional processing (see Roiser et al., 2012, for a review). These tests are usually variants of cold cognitive assessments, adapted to include emotionally valenced stimuli—for example, memory tests in which the stimuli are emotional pictures, or categorization tests that ask subjects to distinguish different types of emotional faces. An important and reliable complementary finding has been that never-depressed individuals generally exhibit positively biased responding, which may reflect a degree of resilience to negative emotional information. Therefore, it is most accurate to state that depressed individuals generally exhibit a *more negatively* biased pattern of responding than healthy volunteers. In some instances, this might be manifested overall as a preferential processing of negative relative to positive stimuli in depression, whereas in others there may simply be no difference in the processing of positive and negative stimuli in depressed individuals, but a marked positive bias in healthy volunteers.

Such negatively biased patterns of responding in depressed individuals, both medicated and not on medications, have been reported on tests of emotional perception (Joormann & Gotlib, 2006), memory (Matt, Vazquez, & Campbell, 1992), attention (Gotlib & Joormann, 2010), and working memory (Joormann & Gotlib, 2008). For example, on the CANTAB Affective Go/No-go test, on which subjects must respond to a specified category of emotional words while inhibiting responses to a different category, Murphy and colleagues (1999) demonstrated that, whereas control individuals responded

slightly more quickly to positive than to negative target words, the converse was true for depressed patients. This pattern was described by the authors as a “mood-congruent processing bias.” Another study using this test identified negative biases in unmedicated depressed individuals (Erickson et al., 2005). Few studies of emotional bias in unaffected relatives of patients with unipolar depression exist, but in general, the findings are consistent with those obtained with depressed individuals (Mannie, Bristow, Harmer, & Cowen, 2007). Other relevant work in this area has identified negative biases in individuals scoring high on neuroticism, which is a risk factor for depression (Chan, Goodwin, & Harmer, 2007; Rijdsdijk et al., 2009). These findings are important from a theoretical perspective because they suggest that basic biases in emotional processing are not simply driven by symptoms, but may instead be important in their genesis (see “A Cognitive Neuropsychological Model of Depression” below).

Findings on tests of emotional bias in bipolar disorder are more mixed, and as might be expected, results vary considerably, depending on the phase of the disorder. In the same study utilizing the Affective Go/No-go test described above (Murphy et al., 1999), manic patients were shown to exhibit a mood-congruent positive bias, responding more quickly to positive stimuli. Attenuated subjective intensity of sad faces (Lennox, Jacob, Calder, Lupson, & Bullmore, 2004) and impaired recognition of negative expressions (Lembke & Ketter, 2002) have also been reported in manic patients. Complementing these results, some studies in bipolar patients have reported negative biases when assessments were administered while the patients were in a depressive episode (Holmes et al., 2008). However, other investigators have failed to find mood-congruent biases in manic (Gray et al., 2006) or depressed (Rubinsztein, Michael,

Underwood, Tempest, & Sahakian, 2006) bipolar patients. Positive biases, negative biases, and null results have all been reported in bipolar patients who were not exhibiting pronounced manic or depressive symptoms at the time of testing (Gopin, Burdick, Derosse, Goldberg, & Malhotra, 2011; Rock, Goodwin, & Harmer, 2010). In samples at genetic risk for bipolar disorder, both positive and negative biases have been reported (Brand et al., 2012; Gotlib, Traill, Montoya, Joormann, & Chang, 2005).

Reward and Punishment Processing in Mood Disorders

In contrast to the extensive literature on emotional biases in mood disorders, abnormalities in reward and punishment processing have received attention only relatively recently (see Eshel & Roiser, 2010, for a comprehensive review relating to unipolar depression). This is surprising, given the conceptual links between reward and punishment processing and several symptoms of mood disorders. Anhedonia, closely related to reward processing, is one of the cardinal symptoms of the depressive syndrome. It is particularly important to understand, as it reliably predicts poorer response to standard antidepressants (Uher et al., 2012). Other symptoms of mood disorders that are likely to be related to reward and punishment processing include difficulty in decision making (in depression) and increased goal-directed activity and excessive engagement in pleasurable activities with potential for harmful consequences (in mania).

Although reward processing has not been studied extensively in patients with mood disorders, some consistent findings have emerged. Importantly, a finding discussed above—that depressed patients are hyper-sensitive to negative feedback (Elliott et al., 1997)—has been confirmed using tasks designed specifically to assess this process, in

both unipolar (Taylor Tavares et al., 2008) and bipolar (Roiser et al., 2009) depressed patients. Other studies reported hypo-sensitivity to positive feedback in unipolar depressed patients (Henriques & Davidson, 2000), or reduced learning from rewarding stimuli (Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012). In euthymic bipolar disorder some investigators have identified hypo-sensitivity to positive feedback (Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008), while others have demonstrated biased learning, depending on whether the most recent episode was manic or depressive (Linke, Sonnekes, & Wessa, 2011).

The studies discussed above utilized tasks on which subjects must learn probabilistic stimulus–outcome associations on a trial-and-error basis. Other tests have probed the impact of explicitly providing information about probabilities, rewards, and punishments during risky decision-making in patients with mood disorders. One of the first studies to examine this question used the CANTAB Cambridge Gambling Task (Rogers et al., 1999), which requires participants initially to choose which of two outcomes they think will occur, and then to stake points on their decision. The subject is informed in advance of the probability of winning. A consistent finding across medicated, unmedicated, and remitted samples is that depressed individuals increase their stake with increasingly better odds (termed “risk adjustment”) to a lesser extent than controls do (Murphy et al., 2001; Rawal, Collishaw, Thapar, & Rice, 2013). Interestingly, impaired risk adjustment has also been reported in bipolar patients in the manic (Murphy et al., 2001) and depressed (Roiser et al., 2009) phases. Bipolar patients also have a greater tendency to bet against the odds on this and other gambling tasks, irrespective of current mood status (Adida et al., 2011; Rubinsztein et al., 2006). Other studies have

demonstrated impaired motivation in unipolar depression, using effort-based tasks where subjects must respond quickly in order to achieve rewards (Treadway, Bossaller, Shelton, & Zald, 2012).

An important development in understanding reward- and punishment-processing in mood disorders (and in neuroscience more generally) is the use of mathematical models to better characterize reward- and punishment-driven behavior. This computational modelling approach involves specifying an algorithm describing how participants are thought to perform the task, and then using this algorithm to predict behavior under different task conditions. The models include a small number of parameters, and patients' parameter values are estimated from their measured behavior (e.g., choices or reaction times). These parameters may then be compared between the groups instead of, or in addition to, the raw data summary statistics such as average reaction time or percent correct. Importantly, these models can distinguish specific aspects of reward processing behavior (e.g., appetite for risk or subjective value of rewards) that would not necessarily be accessible using standard analyses of the raw data (Montague, Dolan, Friston, & Dayan, 2012).

Using such a computational approach, Chase and colleagues (2010) demonstrated that reward learning on a probabilistic task was not specifically impaired in depression per se, but instead was associated with anhedonia in non-depressed as well as in depressed individuals. In a reanalysis of previously published data, Huys, Pizzagalli, Bogdan, and Dayan (2013) built a sophisticated model to demonstrate that a deficit in sensitivity to feedback, rather than reduced learning, better explained observed differences in reward processing between depressed and non-depressed participants.

Their results, obtained on the task employed by Pizzagalli et al. (2008), also indicated that anhedonia, as much as depression, accounted for the findings.

A Cognitive Neuropsychological Model of Depression

An important theoretical implication of the abnormal information-processing findings in mood disorders highlighted in this chapter relates to neurocognitive models of the causes of depressive symptoms. In the classic cognitive model of depression proposed by Beck (1967), depression results from stable, self-reinforcing, dysfunctional negative schemata, which are established as a result of early life experience and targeted by psychotherapeutic approaches such as CBT. This model explains emotional biases and disrupted reward processing in depression in terms of top-down influences from schemata, or what could be conceptualized as “negative expectations.” In other words, depressed individuals exhibit slower responses to happy words (Erickson et al., 2005), or misinterpret facial expressions as sad (Joormann & Gotlib, 2006), precisely because they expect to encounter a negative environment. According to this account, “schematic processing” results in more efficient processing of negative stimuli, resulting in biased reaction times, memories, or choices. Such negative expectations, which include dysfunctional attitudes and negative attributional styles, may be considered a form of “top-down” hot cognition. Interventions such as CBT focus on breaking negative schemata; for example, through challenging their logic, a process that could be conceptualized as training depressed individuals to exert cold cognitive control over their top-down negative biases.

This classical cognitive perspective does not explicitly incorporate any role for the neurotransmitter systems targeted by antidepressant drugs, such as serotonin,

noradrenaline, and dopamine, in the pathogenesis of depressive symptoms. However, there is clear evidence that transmission in these neuromodulator systems can profoundly influence the bottom-up processing of emotional stimuli, instantiating what could be conceptualized as “negative perceptions.” Manipulating monoamine transmission experimentally can alter reward and emotional processing biases, in both healthy volunteers and depressed individuals (Roiser et al., 2005; Roiser et al., 2008). Similarly, genetic variants that affect these systems (e.g., the serotonin transporter linked polymorphic region: 5-HTTLPR) are associated with biased emotional information and reward processing (Fox, Ridgwell, & Ashwin, 2009). According to this account, negative biases occur in depression due to disrupted monoamine modulation of the critical neural circuits that process incoming emotional stimuli (Harmer, Goodwin, & Cowen, 2009). Harmer and colleagues have proposed that it is precisely these kinds of bottom-up biases that are targeted directly by antidepressant drug treatment, allowing the gradual resolution of symptoms over time (see Harmer et al., 2009, and Chapter 18).

Our cognitive neuropsychological model of depression (Roiser et al., 2012) proposes an integrated approach, accommodating both the classical high-level cognitive framework and more recent psychopharmacological findings. In both the classic cognitive model and our neuropsychological model, negative schemata play a central role, but their origins are different in the two frameworks. We propose that bottom-up biases (negative perceptions), influenced by disrupted monoamine transmission, play a causal role in the development of dysfunctional negative schemata, but that the latter themselves also engender top-down biases (negative expectations), which contribute to the maintenance of schemata. The cognitive neuropsychological model also proposes a

central role for a type of impaired cold cognition in depression, executive function: negative perceptions may feed and maintain dysfunctional negative schemata especially when executive function is impaired. Importantly, these different cognitive processes (negative perceptions, negative expectations, and executive function) are probably instantiated via the (dysfunctional) operation of separate, but interacting, neural circuits.

Importantly, this model can be used to understand different types of treatment approaches in depression. As explained in greater detail in Chapter 18, in this model, antidepressants can be understood as primarily influencing biased, hot, bottom-up processing (negative perceptions), thereby reducing or eliminating the occurrence of negatively biased inputs that had been reinforcing the depressed individual's dysfunctional negative schemata. In this way, the contents of the negative schemata may be resolved indirectly. But schemata may not resolve by themselves if impairment in executive function remains, and there is little evidence that antidepressants improve cold cognition. This may explain why cognitive enhancers, as well as rTMS and tDCS of the prefrontal cortex, can augment the response to antidepressant drug treatment. By contrast, psychotherapy (especially CBT) in this model is conceptualized as directly targeting biased top-down processing (negative expectations), through altering negative schemata. However, resolution of schemata may be difficult if their negatively biased inputs remain intact.

If our model is correct, and different treatment modalities address complementary aspects of negatively biased processing in depression, this may provide an explanation for why antidepressants and CBT in combination are more effective than either in isolation, at least in the short run (Forand, DeRubeis, & Amsterdam, 2013). Moreover,

insofar as patients may differ in the presence and malleability of top-down versus bottom-up hot processing, this model could provide a heuristic that will guide research into why different patients may respond to different treatments. Finally, this model can account for the effects of a novel surgical intervention, deep brain stimulation (DBS), in the subgenual anterior cingulate cortex. Neuroimaging studies suggest that this region, which shares strong reciprocal connections with the amygdala and is part of the brain's basic emotional processing circuitry, plays a critical role in instantiating bottom-up negative biases in depression (see Grimm et al., 2009, and Chapter 19) and even operates abnormally in genetically at-risk individuals (O'Nions, Dolan, & Roiser, 2011). Therefore, DBS may alter bottom-up negative biases in depression directly by manipulating the brain circuits that subserve them.

Conclusion

This chapter has reviewed evidence supporting the roles of both hot (emotion-dependent) and cold (emotion-independent) information processing in mood disorders. Unipolar and bipolar patients exhibit reliable impairments on cold neuropsychological tests, and the presence of such impairments during remission and in patients' unaffected first-degree relatives suggests that these are not simply epiphenomena of extreme mood states. Mood-congruent emotional and reward biases are commonly reported in mood disorders, and the finding that these can be altered directly by pharmacological intervention suggests that they result primarily from bottom-up influences. Our neuropsychological model of depression (Roiser et al., 2012) provides an integrated account of disrupted hot and cold cognition in depression. It also has implications for understanding established treatments such as psychotherapy and medication, as well as novel brain stimulation-based

treatments such as rTMS, tDCS, and DBS. This perspective encourages us to take a holistic approach to treatment, including pharmacological, psychological, and psychosocial methods, to improve functional outcome and to prevent depression from becoming chronic and relapsing. Abnormal hot and cold information processing could be used as a form of early screening (Owens et al., 2012), since 75% of mental health disorders start before the age of 24 (Kessler et al., 2005). This would facilitate earlier treatment or even the prevention of depression, stopping it from becoming a lifelong disorder that robs people of their mental capacity and well-being (Beddington et al., 2008).

Future Directions

Mitigating cold cognitive dysfunction in mood disorders is an unmet need, especially in treatment-resistant patients. It will be important to test whether boosting executive function pharmacologically is clinically useful in large-scale trials. It also remains unclear whether cold cognitive impairment predicts poor response to psychotherapy, and whether cognitive dysfunction could be used to predict the onset of mood disorders in high-risk individuals. As well as providing important clinically relevant information, studies addressing these questions would test a central prediction of the cognitive neuropsychological model: that cold cognitive impairment is a cause, as opposed to a consequence, of symptoms. With respect to hot cognition, the cognitive neuropsychological model suggests that it may be possible to predict which patients are most likely to respond to pharmacological versus psychological treatments, by measuring bottom-up and top-down hot cognitive biases. Finally, currently used antidepressants generally have little direct impact on the brain's dopamine system, which plays a critical

role in reward processing. There is a clear rationale for developing dopamine-based treatments to improve symptoms related to motivational processing and decision-making.

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