Understanding depression: A translational approach

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Understanding Depression

A translational approach

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Chapter 3

Explaining depression: neuroscience is not enough, evolution is essential

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Neuroscience provides proximate explanations based on mechanisms, but a full biological explanation of depression also requires an evolutionary explanation of the origins and functions of the capacity for low mood. Failure to recognize that both are essential slows progress. Mood regulates patterns of investment as a function of environmental propitiousness. When investments are not resulting in progress towards a goal, low mood gives a fitness advantage. If a person cannot give up an unreachable goal, low mood can escalate to clinical depression. There are several evolutionary reasons why brain systems that regulate mood are vulnerable to dysfunction.

Introduction

In the course of research for a book on why natural selection has left humans so vulnerable to depression, I asked three leading neuroscientists why the capacity for depression exists at all. One suggested that groups with a mix of optimists and pessimists do better than other groups. A second said that negative mood is harmful while good mood gets people to want to have sex and do other things that increase fitness. A third said that depression results from neurotransmitter-receptor abnormalities.

These responses suggest that even some of the best neuroscientists are unfamiliar with evolutionary principles that long ago transformed behavioural biology. Evolutionary explanations based on benefits to the group have been recognized as problematic for 40 years (Williams, 1966). The belief that positive emotions are useful but negative emotions are harmful is an illusion (Nesse, 2004). Finally, reductionist explanations for why some individuals get depressed do not address the question of why depression exists (Kendler, 2005).

Perhaps more important than specific misunderstandings, however, is the larger problem of widespread failure to recognize that biological traits need both evolutionary and proximate explanations. Neuroscience can never provide a full biological explanation for depression, it can only explain mechanisms. Progress will speed up when we concurrently address the evolutionary question of why depression exists at all. This thesis is supported by considering how the application of how three simple evolutionary principles can advance depression research. The first principle is that proximate explanations based on brain mechanisms are insufficient; every trait also needs an evolutionary explanation. The second is that diseases do not have evolutionary explanations, however evolution can explain why some aspects of the body have been left vulnerable to failure. Third, many symptoms, such as pain, fever, cough, and negative emotions, are not usually the result of bodily defects, they are adaptive responses shaped by natural selection. The brain mechanisms that regulate these responses are vulnerable to dysregulation; we need to find out why.

Proximate and evolutionary questions

Asking evolutionary as well as proximate questions long ago transformed the study of animal behaviour (Alcock, 2005; Alcock and Sherman, 1994; Dewsbury, 1999; Krebs and Davies, 1984). The crucial advance was Tinbergen's (1963) observation that a full biological explanation of any trait requires answers to four questions: two proximate and two evolutionary (Box 3.1). Modern animal-behaviour texts begin with these four questions (Alcock, 1993; Beckhoff and Allen, 1995; Krebs and Davies, 1997), but with a few exceptions (Gazzaniga, 2004); neuroscience texts do not mention them.

As Tinbergen and Mayr emphasized (Dewsbury, 1999; Mayr, 1982; Tinbergen, 1963), proximate and evolutionary questions are not alternatives; answers to both are essential for any complete explanation. Proximate explanations describe the mechanistic details of a trait – its composition and structure at all levels, how the mechanism works, and how it arises in the course of ontogeny. Evolutionary explanations describe how a trait came to be the way it is – the historical sequence of previous traits and the evolutionary forces that shaped the trait. For instance, a proximate explanation for the human locus coeruleus includes the details of its anatomy, chemistry, connections, and its developmental origins. An evolutionary explanation describes its phylogeny, and how its functions give a selective advantage (presumably by regulating noradrenergic transmission and coordinating the emergency response).

Evolutionary hypotheses in neuroscience

Much neuroscience is devoted to studies of adaptive function, however only rarely are such studies recognized as tests of evolutionary hypotheses about how a trait influences fitness (Box 3.2). Instead, neural components are often presumed to have specific functions – as parts of the 'brain as a machine'. This approach has generated much knowledge, but it can be misleading (Childs, 1999; Nesse and Stearns, 2008). Machines have discrete parts engineered to serve one or a few functions. Organisms are products of sequential tiny changes over millions of generations that result in partially differentiated components that may serve many functions. They are hard to reverse engineer because they were not designed by an engineer. Far from implying that traits are perfect, an evolutionary approach shows why many of the body's 'design' are botched, at best (Crespi, 2000; Nesse, 2005b; Nesse and Williams, 1994; Williams, 1996; Williams and Nesse, 1991). An evolutionary view suggests that we should expect evolved brains to be jumbles of incompletely differentiated, jury-rigged parts with multiple overlapping functions.

One conclusion is that few brain structures should have only one or two specific clearly describable functions. Instead, multiple actions, which may or may not correspond to our notions of functions, are distributed across many cross-connected incompletely differentiated structures.

Box 3.1 Tinbergen's four questions (Tinbergen, 1963)

Two proximate questions (about mechanisms)

1. Mechanism – What are the trait's components and how do they work?
2. Ontogeny – What is the ontogeny of this trait?

Two evolutionary questions (about origins)

3. Phylogeny – What is the phylogeny of this trait?
4. Adaptive function – What selective advantages/costs and other evolutionary factors shaped this trait?

Box 3.2 Testing evolutionary hypotheses

Like other scientific hypotheses, proposals about a trait's evolutionary origins or functions can be easy, difficult, or temporarily impossible to test. A controversy that began with Gould and Lewontin's critique of 'adaptationist' thinking (1979) has been both helpful and harmful. The benefit is increased attention to all potential explanations, including genetic drift and other evolutionary factors other than natural selection (Pigliucci and Kaplan, 2000). The cost is a widespread misimpression that evolutionary hypotheses are untestable, 'just-so-stories'. This notion persists despite many effective rebuttals (Alcock, 1998; Borgia, 1994; Queller, 1995; Selzer, 1993)

The issue arises in large part because proximate scientists are unfamiliar with the methods used to test evolutionary hypotheses (Alcock, 2005; Mace et al. 2003; Mayr, 1983; Nesse, 1999d; Reeve and Sherman, 1993; Rose and Lauder, 1996; Stearns and Hoekstra, 2005;). When applicable, the comparative method is strong (Pagel, 1994). For instance, the shape and size of beaks in different species of finches correlates well with the kinds of foods available, and when only harder seeds are available, beaks become thicker in just a few generations (Grant, 1999). Only rarely do neuroscientists have access to data that allow such comparisons (Butler and Hodos, 1996; Glenn Northcutt and Kaas, 1995; Panksepp et al. 2002).

Extirpation is a mainstay for physiological studies of function; take out an organ and see what goes wrong. From the studies of patients with localized brain damage to knock-out mice or aspiration of brain structures, neuroscientists routinely test hypotheses about the adaptive functions of genes (Alcock, 2005; Mayr, 1983; Rose and Lauder, 1996b), neurotransmitters, receptors, and brain structures (Bloom, 1994; Gazzaniga, 1995; Kandel et al. 2000). Such studies are rarely recognized as tests of evolutionary hypotheses about adaptive functions.

Assessing form in relation to function is a mainstay in general biology, where its challenges are recognized. When the details of a trait exactly match those that would well serve a function, that is useful evidence. Stronger evidence is provided by predicting previously unobserved details. For behavioural traits, the situations that elicit the behaviour may provide the best available evidence.

The distributed regulation of motivation offers a good example (Berridge, 2004). Other chapters in this volume illustrate both the value and the difficulties of trying to localize functions. This is discouraging to the goal of fully understanding the brain, but it helps to explain why neuroscience is so difficult. It is not just because the systems are complex, but because the brain's components and connections do not have a coherent organization of the sort found in human-designed machines. Bodies are not irreducibly complex, but some aspects may be indescribably complex.

Many studies address the functions of neurotransmitters and receptors in depression and other disorders (Barnes and Sharp, 1999). Most propose one or a few functions for each transmitter or receptor, sometimes framed in terms of effects on other neural structures, and sometimes in terms of effects on cognition or behaviour. Dopamine, for instance, has long been said to mediate motivation and reward. On deeper analysis this turns out to be far too simple (Berridge, 2004; Salamone et al. 2005; Wise, 2004).

An evolutionary approach provides a different perspective on the origins of traits in conjunction with functions. For instance, duplication of receptor or transmitter genes can give advantages by allowing more exact control of different tissues (Fryxell, 1995; Roth et al. 1982). The pro-opiomelanocortin (POMC) gene was duplicated before the appearance of the jawed fish, thus paving the way for receptor differentiation and further transmitter specialization. Tissue-specific actions

for POMC peptides now differ in different species (Takahashi and Kawauchi, 2006). Differentiation of function in different tissues gives the selective advantage that drives this process, however the functions that are served by different opiods and MSH's are multiple and hard to describe.

The animal behaviour literature contains extensive discussions about how to specify objects of evolutionary explanation, and how to pose and test specific hypotheses (Alcock, 2005; Reeve and Sherman, 1993; Rose and Lauder, 1996). Debates continue, but they are settling down, at least about core issues (Alcock, 2001; Rose and Lauder, 1996; Segerstråle, 2000). In neuroscience the topic is curiously neglected; I suspect this is because there is incomplete recognition that proximate and evolutionary questions are separate, and because some neuroscientists, having never been exposed to the methods for testing such hypotheses, proceed as if data on proximate mechanisms can answer such questions.

Evolutionary explanations for diseases

An evolutionary approach to depression does not mean proposing that depressive disorders are useful. Attempts to find direct evolutionary explanations for a disease are misguided because natural selection does not shape diseases. Selection and genetic drift can, however, explain aspects of the body that leave it vulnerable to a disease, such as wisdom teeth, a small birth canal, and a low anxiety threshold (Williams and Nesse, 1991). Asking and answering such questions has contributed to the rapid growth of evolutionary medicine (http://evmedreview.com, 2008; Nesse and Stearns, 2008; Nesse and Williams, 1994; Stearns and Ebert, 2001; Stearns and Koella, 2007; Stearns et al. 2007; Trevathan et al. 2008). Much progress has been made in discovering why aging occurs (Finch, 2007), why natural selection has not resulted in better protection against cancer (Frank, 2007; Greaves, 2002), and why we are so vulnerable to anxiety (McGuire and Troisi, 1998; Nesse, 1999a).

There are six evolutionary reasons why a trait may have 'design' features that leave bodies vulnerable to a disease (Box 3.3). For a list, see the text box below, for details, see primary sources (Evolution and Medicine Review, 2008; Nesse and Stearns, 2008; Nesse and Williams, 1994; Stearns and Ebert, 2001; Stearns and Koella, 2007; Stearns et al. 2007; Trevathan et al. 2008). The last item, adaptive responses, is not really a reason for vulnerability, but it belongs on the list because responses such as pain, cough, and fever are sometimes confused with diseases. They are responses useful in specific circumstances; selection has shaped systems that express the response when they detect cues associated with those circumstances. For instance, lipolysaccharide (LPS), whose presence is strongly correlated with a bacterial infection, arouses an inflammatory response.

Explaining vulnerability to one disease may require several kinds of explanations. For instance, vulnerability to atherosclerosis results from a combination of mismatch, pathogen evolution, constraints and tradeoffs and adaptive responses (Nesse and Weder, 2007).

The first task in an evolutionary analysis of a medical condition is to determine if it arises directly from a bodily defect or if it is an adaptive response to a more fundamental problem. For example, paralysis, seizures, hallucinations, and cancer are direct manifestations of bodily defects. They have no utility. In contrast, pain, fever, cough, and anxiety are not defects or diseases, they are adaptive responses to more fundamental problems (Nesse, 2005c).

Why are such reactions so aversive? Imagine if they were not. A few rare people have a congenital inability to experience pain. They are almost all dead by early adulthood (Rosemberg et al. 1994; Sternbach, 1963). The experience of pain means something is wrong, but the capacity for pain is an essential adaptation. What about anxiety? Patients with too much anxiety crowd clinics. Those with hypophobia don't complain, but some get into trouble and others die young (Lee et al. 2006).

Box 3.3 Six evolutionary explanations for vulnerability

1. Infection by agents that evolve faster than we do
2. Mismatch between our bodies and novel environments
3. Constraints on what selection can do
4. Tradeoffs that limit the perfection of any trait
5. Traits that increase reproduction at the expense of health
6. Protective responses such as pain, fever, cough, and anxiety

Like everything else in the body, the mechanisms that regulate protective responses can fail, causing conditions such as chronic pain and anxiety disorders. Even responses from intact regulation mechanisms can cause problems. For instance, fever can result in seizures, and diarrhoea can cause dehydration and death. These dire consequences seem to suggest that natural selection has done a poor job of shaping the regulation mechanisms. The relative safety of using drugs to block fever, cough, and diarrhoea further suggests that natural selection may not be able to shape effective regulation mechanisms.

However, false alarms are normal and inevitable for bodily defences. A full analysis of the optimal threshold for expressing a defence requires signal detection theory (Nesse, 2005c). In general, however, the cost of a false alarm is likely to be small compared to the cost of failing to activate the protective state when it is needed, so the optimal response threshold results in many false alarms. Fleeing in response to the sound of a breaking twig costs only a few calories. Not fleeing may be infinitely costly if the sound was made by a lion. False alarms are normal and common. This is the 'smoke detector principle' (Nesse, 2005c).

As with other diseases, serious depression is not an adaptation shaped by natural selection. It has no evolutionary explanation. However, we do need an evolutionary explanation for why natural selection has left us so vulnerable to a disease as common and devastating as depression. Some abnormal depression is related to normal low mood, so explaining the origins and functions of mood is an essential foundation for understanding depression.

The utility of emotions and mood

Emotions and moods give organisms a selective advantage by adjusting physiological and cognitive parameters to deal with situations that have repeatedly influenced fitness over the course of evolution (Ekman, 1992; Keltner et al. 2006; Nesse, 1990; Panksepp, 1998; Plutchik, 2003; Tooby and Cosmides, 1990). Moods are longer in duration and less tightly tied to specific cues than emotions, but both are special modes for coping with certain situations (Nesse, 1999c; 2006, Thayer, 1996). Single-celled organisms have two behaviours: move towards resources or away from danger (Adler, 1966; Larsen et al. 1974). From these primal origins, behavioural activation (BAS) and behavioural inhibition (BIS) brain systems developed; they increase fitness in situations characterized by opportunity/gain or threat/loss, respectively (Barrett, 2006; Gray, 1987; Watson et al. 1988).

Moods and emotions are almost all positive or negative because neutral situations do not influence fitness (Barrett, 2006; Nesse, 1990; 1999c). Natural selection has differentiated generic positive and negative states into more specialized emotions that are helpful (on average) in the specific situations that a species has encountered (Nesse, 2004; Plutchik, 1980). The so-called 'basic emotions' correspond to especially common well-defined situations, such as threat (for anxiety) and gaining valued resources (for joy).

Positive emotions seem more useful than negative ones because they are elicited in propitious situations. In situations involving threat or loss, negative moods and emotions are more useful. They adjust physiology, motivation, and behaviour to cope with such situations involving threats or losses (Nesse, 1990; 1999c; Plutchik, 2003; Tooby and Cosmides, 1990). For instance, Walter Cannon long ago recognized the utility of the emergency response in situations that required fight or flight (Cannon, 1914). This emergency system has false alarms; when recurrent, they are called panic disorder (Nesse, 1987).

Depression

Much neuroscience research proceeds on the assumption that 'depression is a brain disease'. This is certainly correct in the sense that all mood and behaviour is mediated by brain mechanisms (Kendler, 2005). In some cases, it is correct in the more specific sense that depression arises from primary brain abnormalities. The slogan has also helped the public to understand that depression is not a personal failing, but a treatable condition.

However, assuming that depression is a brain disease limits scientific progress in several ways (Kendler, 2005; Moncrieff, 2007). First, it implies that genetic and brain variations that predispose to depression are abnormalities, when they may be neutral, or even advantageous, in certain environments. Second, it neglects the role of life events and other causal factors that interact with brain variations to cause most depression. Third, it implies that depression symptoms are pathological, distracting attention from the task of finding the functions for normal low mood. Fourth, it implies that brain changes associated with depression are abnormalities, although they can equally well reflect the normal actions of mechanisms that mediate mood (Halbreich, 2006; Mayberg et al. 1999). Finally, diagnostic criteria based only on symptoms encourage studying major depression as if it is one condition with one aetiology, although it can have many different aetiologies (Antonijevic, 2006; Keller and Nesse, 2005; Kendler, 2005).

In contrast, an evolutionary perspective recognizes that depression symptoms can be normal or abnormal depending on the situation (Horwitz and Wakefield, 2007), that multiple factors may combine to cause a single case of depression, that etiological factors may differ markedly from case to case (Nesse, 2006), and that different depression symptoms may have been shaped to cope with different precipitating situations (Keller and Nesse, 2006a). Before even addressing aetiology – proximate explanations for why one person gets pathological depression and another does not – an evolutionary approach addresses the more fundamental questions of why the capacity for low mood exists at all, how it is normally regulated, and how it is related to some cases of depression.

Is mood an adaptation? General evidence

The hypothesis that the capacity for mood is normal and useful is supported by its universality, as contrasted with abnormal phenomena such as seizures and hallucinations that most people never experience. So many people now assume that 'depression' refers to an abnormal state that the phrases low mood and high mood are adopted here to describe the range from despair to elation without any implication of normality or abnormality.

Stronger evidence that the capacity for mood is an adaptation is provided by the close regulation of mood by the fitness implications of a situation. Fast progress towards a valued resource elicits positive mood; lack of progress lowers mood. Selection can shape regulation systems only for traits important to fitness, such as breathing and anxiety. The stimuli that influence mood are less tangible than those that regulate breathing, but there is no doubt that mood is carefully regulated (Brown and Harris, 1978; Larsen, 2000; Monroe and Simons, 1991; Thayer, 1996).

Direct evidence for the utility of a response is provided by individuals who lack the capacity. For instance, and as discussed above, individuals born with no capacity for pain experience accumulating damage that causes death by early adulthood (Rosemberg et al. 1994; Sternbach, 1963). It would be difficult to distinguish individuals who lack low mood from the merely fortunate. Nonetheless, if mood is useful, then individuals who lack a capacity for low mood have a disorder. If and when we discover drugs that reliably block low mood, this will make it possible to study the functions of low mood directly. In the meanwhile, insight comes from the problems caused by hypomania (Doran, 2008). Inability to experience low mood results not only in social complications, but also in tendencies to make impulsive decisions and to start too many projects. Whether it results in persisting too long in fruitless enterprises is yet to be conformed.

The evolutionary origins of low mood

The above background guides correct formulation of the core question: In what kinds of situations arising repeatedly over evolutionary history would individuals with a capacity for low mood get a fitness advantage? On the face of it, pessimism, lack of initiative, low self-worth, and fatigue seem worse than useless. However, in situations when all possible actions will bring costs greater than benefits, the best thing to do is . . . nothing.

A seminal article by Klinger (1975) initiated modern work on mood as an adaptation that regulates goal pursuit. He noted that rapid progress towards a goal arouses high mood that motivates continued effort and risk-taking. When efforts to reach a goal are failing, low mood motivates pulling back to conserve resources and reconsider options. If conditions do not improve and no other strategy is viable, low mood disengages motivation from the unreachable goal so efforts can be turned to more productive activities. If the individual persists in pursuing an unreachable goal, ordinary negative affect can escalate into pathological depression.

In a series of articles (1983; 1990) and a book (1998), Carver and Scheier outline a control theory model supported by experimental data showing that mood is influenced mainly, not by levels of resources or payoffs, but by the rate of approach to a goal. In a particularly important finding, negative mood is aroused more readily by obstacles encountered in pursuit of positive goals than it is by the inability to escape dangers (Carver, 2004). This challenges models for depression based only on stress and losses (Blanchard et al. 1993), and suggests deeper attention to personal goals and the BAS.

Many are now studying the exigencies that arise in the pursuit of personal goals (Emmons, 1999; Emmons and King, 1988; Little, 2000). Klinger calls these 'current concerns', Little calls them problems arising in 'personal projects' (Little, 2006), while others focus on 'possible selves' (Cantor, 1990; Oyserman and Markus, 1990). Studies of the life course document increasing distress as it becomes apparent that a goal, such as having children, will not be met. When the goal is finally given up, negative affect decreases abruptly (Heckhausen et al. 2001). Other studies show that the impact of a life event depends profoundly on an individual's values (Diener and Fujita, 1995), and life context (Brown and Harris, 1978; Finlay-Jones and Brown, 1981; Monroe and Simons, 1991).

Why do people persist in pursuing unreachable goals? Each of several reasons is a different pathway to depression. Extreme ambition may leave a person dissatisfied even with exceptional achievements. A wish to please everyone is a common unreachable goal, as is trying to reform an abusive or alcoholic partner. Anxiety can prevent taking the risks necessary to escape an untenable life situation. Even without these factors, many people find themselves trapped pursuing an unattainable goal. The word 'goal' suggests tangible things such as getting a job, but many of life's largest goals are more personal, such as getting a spouse to be affectionate, finding sexual satisfaction,

pleasing a parent, becoming recognized as a poet, or helping a child to get off drugs. Giving up such goals can mean giving up what gives meaning to life and a social identity.

Individuals differ in their general ability to disengage from unreachable goals (Wrosch and Scheier, 2003). Those more capable of giving up are less prone to low mood, as are those who reengage more quickly after a loss (Wrosch et al. 2003). These findings challenge the conventional wisdom that persistence is always wise, and they suggest studies to determine whether depression remission often follows finding a new strategy or giving up a goal. Existing evidence finds depression much more prevalent in women who have experienced a 'fresh start' event (Brown et al. 1992).

The general idea that low mood arises when desires cannot be satisfied is by no means new (Nussbaum, 1994). What is new is trying to understand how the capacity for mood was shaped by its ability to increase fitness in certain situations. The most general answer is: *mood regulates patterns of resource investment as a function of propitiousness* (Nesse, 1991; 1999b; 2000). In a propitious environment, small investments offer big payoffs, so high mood and risk-taking increase fitness. In an unpropitious environment, costs and risks are greater than benefits, so low mood and anxiety increase fitness.

Payoffs vary across time and projects. As one activity continues, such as foraging, marginal benefits decline. When benefits from the current activity become lower than those for an alternative, behaviour shifts to the next activity. Charnov's marginal value theorem shows that the optimal time for an animal to quit foraging in one location and move to another is when the rate of return from the current patch declines below the average rate of return over several patches (1976). Scores of experiments show that even simple organisms make good decisions about when to move to a new patch (Real and Caraco, 1986; Stephens and Krebs, 1986). Related mechanisms regulate the decision to quit foraging altogether. As the evening air cools, bumblebees eventually spend more calories per minute than they gain. At that point, the best thing to do is to stop and wait for more propitious conditions (Heinrich, 1979).

Humans are more complicated. We pursue multiple long-term goals simultaneously. Success depends on judiciously allocating effort among diverse enterprises, including getting material resources, getting and keeping a partner, taking care of children, making and keeping friends, and gaining social status. They often conflict, so life is difficult. When a strategy is not working, low mood disengages effort and motivates consideration of other ways to reach the goal (Gut, 1989). If no strategy seems likely to work, motivation disengages from that enterprise, and shifts effort to another. If pursuit of an unreachable goal continues, ordinary low mood can escalate into severe depression (Gut, 1989; Klinger, 1975).

Note that low mood is elicited not by stress or losses, but by inability to make progress towards an important goal. After a loss, sadness can improve coping and prevent additional losses (Nesse, 2005a). Sadness and low mood are phenomenologically similar, and they are often associated because losses often disrupt strategies for getting crucial resources, but they correspond to different situations.

Anxiety and low mood are also highly comorbid. When loss is likely, anxiety is useful. Failing efforts to preserve a major life enterprise, such as a marriage or a job, are likely to arouse anxiety (because of the threat of loss) and low mood (because efforts to prevent the loss are failing). Comorbidity of depression and anxiety can also arise from the risks of leaving an intolerable job or marriage (Maser and Cloninger, 1990).

The above generic theory has several more domain-specific versions. One group, starting from ethological observations (Price, 1967), has emphasized an inability to yield in status competitions as the crucial situation that gives rise to depression (Gilbert, 1992; Gilbert and Allan, 1998; Price and Sloman, 1987; Price et al. 1994). They interpret depression as 'involuntary yielding behavior'

that stops attacks by dominants. This makes important links with social competition (Price et al. 1994) and it helps to explain social aspects of depression symptoms, such as low self-esteem. It is also supported by reanalyses of life events data showing that depression is precipitated not by stress in general, but by events that involve being trapped or humiliated (Brown et al. 1995; Kendler et al. 2003). So far, we lack data on what percentage of depressions arise mainly from losing status competitions.

Watson and Andrews (2002) have suggested that depression guides 'social navigation' by manipulating others. They also suggest that depression can focus cognitive effort on solving social problems, an idea also proposed by Gut (1989) and Bibring (1953). Hagen argues that depression itself and even suicidal tendencies are adaptations to manipulate others to get resources at crucial times such as birth of a child (2002). Allen and Badcock (2003) argue that depression is useful in situations that involve high risk of exclusion from a social group, to signal submission and motivate actions that will make one accepted by the group. These views have been criticized by Nettle (2004) who argues, as I do, that serious depression is rarely useful. He instead emphasizes the vulnerability of any system that depends on many genes (Keller and Miller, 2006) and the possibility that tendencies to negative emotions may have been selected because they motivate high ambition (Ross et al. 2001).

The different subtypes of anxiety aroused by different dangers (Marks and Nesse, 1994) suggests that selection could also have shaped subtypes of depression to deal with problems in different domains. Data confirming this nonobvious prediction support the more general hypothesis that depression symptoms are adaptive. Two preliminary studies found significant differences in depression symptoms depending on the precipitant (Keller and Nesse, 2005; 2006b). Not only are the symptoms remarkably different depending on the cause, the patterns are congruent with functional expectations. In a larger replication, bereavement and romantic break-ups were associated with sadness, anhedonia, appetite loss, and guilt, while chronic stress and failures were associated with fatigue and hypersomnia (Keller et al. 2007b). If different depression symptoms have different functions, studying depression as a single syndrome may conceal more important phenomena.

Why so vulnerable?

Over 10% of people in the United States experience serious depression, many during early adulthood when other chronic diseases are rare (Kessler et al. 1997). Why has natural selection left the mood regulation system so vulnerable to failure? Each of the six categories from Darwinian medicine (Nesse and Williams, 1994) offers possible explanations (see text box 3.3).

Modern environments may increase the risk of depression, although no reliable data allow comparisons with hunter-gatherer populations (Cordain et al. 2002). Depressogenic situations may be especially common in modern life because goals are far larger and longer in duration than those the regulation mechanism was shaped for (Nesse, 2000). Physical factors such as artificial light, and changes in exercise and diet that can directly influence brain mechanisms also deserve consideration (Frasure-Smith et al. 2004).

Infectious causes are likely given the link between inflammatory cytokines and depression (Pollak and Yirmiya, 2002; Schiepers et al. 2005). A large literature documents the utility of 'sickness behavior' in animals (Hart, 1990). During an infection, effort and conflict are best avoided. Specific organisms are rarely identified, although Borna virus may cause a few cases (Bode and Ludwig, 2003). Another factor may be autoimmune reactions resulting from lack of childhood exposure to the diversity of pathogens found in more natural human environments (Rook and Lowry, 2008).

Constraints on what selection can accomplish are relevant. For instance, complex traits such as the ability to regulate mood, tend to have high variance that leaves some individuals at pathological extremes (Keller and Miller, 2006).

Tradeoffs are probably important. Low mood has costs, lost opportunities at the very least. Inappropriate high mood results in taking risks and wasting energy that may have been even more costly. Vulnerability to depression could also result if individuals who struggle especially hard to avoid failure tend, on average, to be especially successful (Nettle, 2004; Ross et al. 2001).

Finally, there is the possibility, emphasized here, that depression is prevalent because human social life routinely results in substantial numbers of individuals getting trapped pursuing unreachable goals. The proportion should vary substantially depending on cultural factors, and this variation may help to explain cultural differences in depression rates.

Why are some people more vulnerable to depression than others? This question at the centre of much neuroscience research, is entirely different from the question of why depression exists, but an evolutionary perspective may be useful nonetheless. One possibility is that differences in baseline mood, and differences in the gain setting for mood regulation systems, may have little influence on fitness. For instance, 5HT-related polymorphisms that increase the risk of depression in response to life events (Caspi et al. 2003), interferon (Kraus et al. 2007), and tryptophan depletion (Jans et al. 2006) may offer benefits in some circumstances; they should not be assumed to be defects (Barr et al. 2004). A polymorphism that is associated with decreased synthesis of IL-6 protects against depression caused by interferon treatment (Bull et al. 2008); one wonders if individuals with this polymorphism might be more vulnerable to infection.

Finally, there is the question of how to understand the effects of stressors on mood regulation mechanisms. They are usually interpreted as 'kindling' (Post and Weiss, 1998) or otherwise damaging the system. However, the body has many facultative adaptations that adapt individuals to their environments. For instance, early heat exposure increases the number of sweat glands. Each additional depression episode seems to reduce the threshold for further episodes (Kendler et al. 2000). This may well reflect damage of the same sort that causes chronic pain. It is conceivable, however, that it is related to a system that adapts the depression threshold based on experience in the social environment.

Bipolar disorder needs a separate analysis, but increasing evidence that many depressives have bipolar tendencies is clearly important (Akiskal, 2003). At the very least, it calls attention to the tight links between the BIS and BAS. A control theory approach suggests the existence of a feedforward mechanism to prevent overshoot by dampening mood even as it rises, and increasing mood soon after it falls (Nesse, 2006). Failure of such a mechanism would explain many aspects of bipolar disorder. It is worth noting that this book dedicates three chapters to bipolar disorder, and in particular to the similarities and dissimilarities between unipolar and bipolar disorders (see Chapters 6, 21, and 22).

Practical implications

While we await stronger conclusions about the evolutionary origins and functions of low mood, an evolutionary approach has practical implications for depression research strategies.

Measure and analyse specific symptoms, not just depression

Diagnostic algorithms collapse multiple variables into a binary datum. Depression scales collapse multiple symptoms into a single continuous variable. If depression was unitary, these data reduction strategies would be sensible. However, different precipitants arouse different symptoms (Keller et al. 2007a), so analysing specific symptoms is essential, as is measuring the domain of the precipitant.

Study etiological subtypes of depression

It has been hard to define depression subtypes based on aetiology, although attempts are being made on the basis of patterns of neuroendocrine changes (Antonijevic, 2006). Basing subtypes on the category of precipitant is a strategy worth considering. Another is to define categories based on the several ways a defensive response can become dysregulated. As shown in the text box below (Box 3.4), a normal regulation mechanism does not guarantee that the response will be useful, and etiological subtypes of depression correspond to different mechanism abnormalities.

Put depression diagnostic criteria on a scientific foundation

The diagnosis of DSM-IV Major Depression ignores context, with the telling exception of grief (American Psychiatric Association, 1994). However, if low mood can be useful, then distinguishing normal from pathological responses requires considering context (Horwitz and Wakefield, 2007; Nesse and Jackson, 2006). Searching systematically for situations that could cause low mood would make the clinical evaluation of depression like that for other medical problems, such as pain, fever, and fatigue, that are investigated by considering what may be arousing the defence.

Gather data on motivational structure

The evidence that severe life events precipitate depression is overwhelming (Brown et al. 1988; Caspi et al. 2003; Finlay-Jones and Brown, 1981; Kessler, 1997; Monroe and Simons, 1991). Research has moved steadily from life event checklists to methods that take account of the individual's life context (Monroe and Simons, 1991; Paykel, 2001). This parallels recognition in psychology that emotions are elicited not just by cues, but by an individual's appraisal of what information means for ability to reach personal goals (Ellsworth, 1991; Scherer et al. 2001).

Behavioural ecology has well-established categories for the resources organisms need: somatic resources (personal health, attractiveness and ability, and material resources), reproductive resources (a mate and offspring), and social resources (allies and status) (Krebs and Davies, 1991). Mood is influenced by an individual's ability to get these resources, the gaps between resources and personal goals, and how individuals cope with these gaps. We need instruments to measure the motivational structure of individuals' lives. Such measures would have immediate applications. For instance, how do individuals trapped pursuing an unreachable goal compare to others on HPA axis abnormalities, agitated depression symptoms, and drug response?

Box 3.4 Etiological subtypes based on regulation mechanism status

1. Regulation mechanism is normal; low mood is useful in this specific instance
2. Regulation mechanism is normal; low mood is useless or harmful in this specific instance
3. Regulation mechanism threshold or gain is abnormal; depression symptoms are excessive or deficient
4. Regulation mechanism is fundamentally abnormal; depression symptoms arise without a precipitant, or in response to a situation that should not lower mood
5. Secondary complications of depression, such as complications of weight loss
6. Depression arising from mechanisms unrelated to those that normally regulate mood

Consider the many ways genes can influence vulnerability

About 40% of the vulnerability to depression can be attributed to genetic differences (Levinson, 2006; Sullivan et al. 2000), however, no locus accounts for more than a few percentage of the variation (Holmans et al. 2007). Epigenetics and heterogeneity offer possible explanations (Caspi et al. 2003; Levinson, 2006). However, thousands of genes influence the brain systems that regulate mood, so polymorphisms at many loci will influence depression vulnerability. Why none have major effects remains a good evolutionary question. One possible answer is that polymorphisms with large effects on mood may have been selected out.

A second implication is that genes may influence depression by complex indirect pathways. One comprehensive developmental model considers 64 pathways (Sullivan et al. 2000), however, other pathways may be even less direct. For instance, diet and exercise influence depression (Duman, 2005), so genetic variations that influence food or exercise preferences (Heller et al. 1988) should influence mood. Likewise, any polymorphism that increases the likelihood of becoming trapped in the pursuit of an unreachable life goal should contribute to depression.

Animal models

The Porsolt test uses rat swimming behaviour to identify promising new drugs; longer swimming is presumed to indicate delayed onset of helplessness (Petit-Demouliere et al. 2005). But when rats stop swimming they do not drown, they just float, a fine adaptive strategy. Rats on antidepressants swim more than is optimal; in a natural environment they would drown sooner (Nadeau, 1999). New strategies for drug discovery may emerge from animal models based on goal pursuit. Animal models of depression are discussed in several chapters of this book (see Chapters 7–12).

Study functional effects of antidepressants

Much research on antidepressants presumes that they normalize some aspect of neurochemistry (Barden et al. 1995). However, if some depression is an excessive response from a normal system, then antidepressants may act by blocking the low mood system at various loci in the same ways that analgesics block pain. Antidepressants usually do not cause euphoria for the same reason that aspirin does not lower body temperature below normal. The common phylogenetic origins of pain, anxiety, and low mood in the BIS may explain why antidepressants tend to be useful for blocking diverse defensive responses. The last chapter of this book (Chapter 27) illustrates the future directions for antidepressants research.

Conclusion

Mainstream research on the causes of depression has been making full use of only one half of biology. Asking evolutionary as well as proximate questions should speed progress, especially for disorders such as depression that can arise from dysregulation of useful responses. The above proposals about specific functions of low mood and its relationship to depression need much more work before they can be considered confirmed. The broad thesis of this article is not that we know why depression exists, it is that seeking the answer will bring major advances.

This perspective is prone to misunderstanding. The utility of some low mood does not imply that we should not treat depression. Quite the contrary. Much of general medicine consists of relieving suffering by blocking pain, cough, and other aversive symptoms even when they are normal responses to a problem whose source is still being sought. Furthermore, the utility of some low mood is fully compatible with the hypothesis that some clinical depression arises from

abnormal brain mechanisms, and most arises from interactions of brain variations with environmental situations. There is nothing radical about an evolutionary approach to mood disorders, and the enterprise should not be viewed as controversial, although straightforward reasoning from well-established evolutionary principles can yield surprising conclusions. More important, it suggests specific new research that is badly needed.

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