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Review

What should animal models of depression model?

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Abstract

In this article, we discuss what animal models of depression should be attempting to 'model'. One must first determine if the goal is to model the regulatory mechanisms by which antidepressant treatments alleviate the various symptoms of depression, or to model the dysregulatory mechanisms underlying the etiology of those symptoms. When modeling the mechanisms of antidepressant effects, a key feature that is often overlooked is the time course required for behavioral efficacy. Even in the clinical literature, there is considerable confusion and inconsistency in defining and identifying 'time of onset' of clinical effect. Although the 'therapeutic lag' may not be as long as has been commonly believed, it does occur. Observable improvement in either global symptomatology or specific symptoms becomes evident after 7–14 days of treatment, and more complete recovery takes considerably longer. Thus, any model addressing potential mechanisms of antidepressant action should exhibit a similar time-dependency. Second, whether attempting to address mechanisms underlying behavioral effects of antidepressants, or the neurobiological substrates underlying the development and manifestation of depression, it is essential to recognize that the syndrome of depression is a diagnostic construct that includes a variety of disparate symptoms, some of which may be related mechanistically, and others that may not be specific to depression, but may cut across categorical diagnostic schemes. Further, it is critical to recognize the close relationship of depression and anxiety. Psychological studies have suggested that the myriad symptoms of depression and anxiety may be subsumed within a more limited number of distinct behavioral dimensions, such as negative affect (neuroticism), positive affect, or physiologic hyperarousal. These dimensions may be related to the functioning of specific neurobiological systems. Thus, rather than trying to recreate or mimic the entire spectrum of symptoms comprising the syndrome of depression, it may be more informative to develop animal models for these behavioral dimensions. Such models may then provide access not only to the neural regulatory mechanisms underlying effective antidepressant treatment, but may also provide clues to the processes underlying the development and manifestation of depression.

Contents

The focus of this article is to ask what we should be attempting to 'model' when we consider animal models of depression. Perhaps the most appropriate definition of 'model' for this context in Webster's Unabridged Dictionary is 'a representation to show the appearance of something.' But with respect to the disease of major depressive disorder (MDD), what is it that we want to represent in animals- the neurobiological underpinnings of the disorder, the entire syndrome, specific symptoms associated with it, prediction of treatment efficacy? And to what end? Given that the etiology (ies) of MDD is unknown and that there is a genetic diathesis for its occurrence (Kendler et al., 1995; Kendler, 1996), although etiologic validity is desirable, it is not a practical criterion for an animal model of MDD at this time.

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By contrast, predictive validity — the ability to make accurate predictions about what happens clinically from the model—is useful specifically with respect to the model's ability to predict the therapeutic efficacy of antidepressants. Even here, though, problems can arise depending on what one expects to gain from such models. Current models, perhaps more appropriately called 'screens,' have been designed to detect most, if not all, existing antidepressants while excluding many non-antidepressants. The mechanism(s) of action by which ADs produce positive results in such 'screens' may not be identical to, or even similar to, the mechanisms underlying their clinical effects. For example, there is a great deal of current interest in the idea that brain derived neurotrophic factor (BDNF) is involved in the mechanism of action of ADs (Duman et al., 1997). A widely used and useful screen for ADs is the forced swim test (Porsolt et al., 1978). This test, and modifications of it (Detke et al., 1995), detect most antidepressants. For this procedure, rats are placed into a cylinder of water at 23–25 °C, of sufficient depth to prevent their feet and tail from touching the bottom. Two swim sessions are carried out, usually separated by 24 h. Typically, the first session is 15 m in duration, and the second 'test' exposure is 5 m. Drugs are administered, usually 2–3 times during the intervening period, oftentimes given shortly (i.e. within 1 h) both after the initial session and before the test session. Compared to vehicle-treated rats, those treated with antidepressant drugs show more active behavior, in particular swimming and struggling, and reduced immobility (i.e. floating) during the test session.

Acute initial administration of BDNF to rats also produces positive results in this test in three days or less (Siuciak et al., 1997; Shirayama et al., 2002). However, standard ADs do not elevate mRNA for BDNF or BDNF protein in the brain of rats unless they are administered for two to three weeks, if they cause any elevation at all (Nibuya et al., 1995; Altar et al., 2003; Coppell et al., 2003). Thus, the mechanism(s) by which standard antidepressants produce positive results in the forced swim test cannot include BDNF, as the temporal sequence is wrong. Of course, this does not mean that BDNF may not be important for the therapeutic effects of ADs in patients. So if we want our model to help us understand the mechanisms by which ADs produce their therapeutic effects, the forced swim test may have limited utility (assuming of course that BDNF is actually involved in therapeutic effects). Alternatively, since we would like to detect novel ADs that may have a different spectrum of action than existing ADs (e.g. having utility in treatment refractory patients), the forced swim test may be useful, again assuming that BDNF or analogs have utility as ADs. Unfortunately, most models with predictive validity seem to be designed to detect either existing or 'me too' drugs rather than those that are truly novel.

Another issue relevant to predictive validity is the time course of drug effects in preclinical screens versus how they are used clinically. Many screens detect antidepressant-like activity in animals quite quickly, within 24 h. Further, the drugs may be given prior to the intervention producing the behavioral alteration and prevent its occurrence rather than reversing it. This bears no similarity to how these drugs are used for acute depressive episodes, when they are administered only after symptoms appear and for months. Although it is widely believed that the *onset* of therapeutic efficacy is delayed for at least several weeks, more recent research casts doubt on this idea. This is discussed in detail later. However, even if it is true that the onset of behavioral improvement occurs earlier than is believed currently, no data exists to indicate that such improvement occurs within a day.

Finally, most models claiming predictive validity do so for treatment effects for an acute depressive episode. As mentioned previously, in some of these models the drugs are given to prevent the behavioral alteration from occurring. Such a treatment regimen would seem more relevant to the well-documented prophylactic effects of essentially all ADs (Frank et al., 1990; see Hirschfeld, 2001). In spite of this, and the established recurrent nature of MDD (see Frank and Thase, 1999), there has been essentially no emphasis on research trying to develop models that might help us understand prophylactic effects. It may well be that those pharmacologic effects producing efficacy for acute depressive episodes are identical to those preventing relapses or recurrences. But this need not be so. Preclinical research aimed at understanding prophylactic effects of ADs is sorely needed.

Earlier research emphasized the notion that an animal model should exhibit behavioral features that are reasonably analogous to the symptoms of MDD (e.g. McKinney et al., 1969), i.e. that they have face validity. Others have suggested that this is not a necessary criterion for an animal model (see Geyer, 1995). Moreover, we would argue that it is conceptually problematic to attempt to reproduce the entire syndrome of MDD, or even to attempt to produce specific 'symptoms' that can be readily observed in animals. MDD is a diagnostic construct, and one that, as a rule, is comorbid with many other psychiatric diagnoses (see Mineka et al., 1998; Devanand, 2002), as well as other medical diseases (see Lydiard, 2001; Kanner and Balabanov, 2002; Katon, 2003; McDonald et al., 2003; Musselman et al., 2003). The 'syndrome' of depression consists of clusters of symptoms reflecting dysregulation of a variety of affective, somatic, and cognitive processes (e.g. emotion, sleep, appetite, motor activity, attention) that are not necessarily specific to MDD. Furthermore, such symptom clusters are likely to reflect dysregulation of larger behavioral dimensions (see, e.g. Mineka et al., 1998, and discussed below). Although there may be some overlap and convergence, it is likely that different brain circuits and neurotransmitter systems are involved in regulating each of these complex behavioral dimensions, some perhaps interactively, others independently. Consequently, attempting to reproduce the majority of symptoms, hoping, perhaps, to

gain some insight into the neurobiology of 'depression', seems misguided at best, misleading at worst. An emphasis on modeling those behavioral dimensions that are dysregulated in depression, rather than reproducing either the entire syndrome or specific symptoms associated with it, may be more useful in this context.

1. Time course of clinical improvement

Some models with predictive validity generate positive results with ADs in 24 h or less after their administration (Horovitz et al., 1965; Porsolt et al., 1978; see Lucki, 1997) whereas more chronic treatment is needed in other models (see Jesberger and Richardson, 1985; see Willner, 1997). It is widely held that the *onset* of therapeutic efficacy in depression takes 2–3 weeks to occur. Thus, it has been debated whether in those models or screens that detect antidepressant- like activity in 24 h or less, the mechanisms responsible are relevant to those underlying clinical efficacy. Given this, it may be useful to review briefly the literature on the onset of AD action in patients.

Although there appears to be consensus that maximal behavioral improvement caused by antidepressants (ADs) takes two to three months to occur, the time it takes for ADs to initiate their behavior effects has become a subject of increasing controversy. A view long held and remaining strong today is that there is a 'lag' period for AD effects, i.e. the 'onset' of drug-induced behavioral improvement may take two to three weeks, or even longer, to occur (Gelenberg and Chesen, 2000). This viewpoint led investigators to study long-term regulatory effects of ADs on monoamine systems (see Lenox and Frazer, 2002) as well as on downstream effects initiated by enhancement of noradrenergic or serotonergic transmission (see Lenox and Frazer, 2002). Much valuable information has been obtained from such studies, some of which have generated ideas of how to develop more 'rapidly acting' ADs (Artigas, 2001). The types of data that have led to the development of the widely-held concept of the 'therapeutic lag' appear to be: (1) the time it takes for drugs to cause significantly greater improvement in global measures of depressive symptomatology than placebo, and (2) 'pattern analysis' of the global response pattern of patients participating in AD trials that concluded that 'true' drug response was characterized by a several-week delay in 'onset' and was persistent, i.e. non-fluctuating (Quitkin et al., 1984, 1987). This latter analysis also contributed to the notion that it is important to wait four or preferably six weeks before non-response to drug can be assumed definitively (Quitkin et al., 1984, 1996).

Factors relevant to both these approaches have been discussed in detail (Preskorn, 1994; Katz et al., 1997) and will only be mentioned briefly here. There is no doubt that early detection of drug effects is complicated by the fact that many depressed patients do respond, at least initially, to placebo. Given this, the parameter that limits detection of drug specific effects is the duration and magnitude of the placebo response (Preskorn, 1994). The conclusions of Quitkin and associates (1984, 1987, 1996) are compromised somewhat by the fact that in the studies they retrospectively reviewed for the pattern analyses (1) many patients did not receive their full dose of AD before the 15th day of treatment and sometimes this even occurred later; (2) over 50% of the patients met criteria for 'atypicality', whereas only about 30% were 'endogenous', and (3) perhaps most importantly, improvement was measure by a global rating scale such that the patient had to be rated as either 'very much improved' or 'much improved', to be judged as improved. Importantly, Parker et al. (2000) has indicated that the incidence plot of a persistent response presented by Quitkin et al. (1996) revealed a statistically significant difference in drug-induced 'trajectories' by two weeks and concluded that these data actually provided evidence of early improvement in responders to antidepressants. It should also be noted that the scales commonly used to measure the severity of depression for purpose of assessing treatment efficacy (e.g. the Hamilton Depression Scale, or HAM-D), evaluate the symptoms occurring over a preceding period of time (e.g. 7 days) and not just at the time of the evaluation. This obviously reduces the temporal sensitivity of any time course analysis.

From the beginning of the clinical evaluation of ADs, a number of studies have appeared that questioned the existence of a substantial lag period for drug-induced behavioral improvement. Some of these studies reported that early improvement was associated with positive treatment outcome; others reported that lack of early behavioral improvement predicted a poor outcome. Unfortunately, none of these studies (e.g. Coryell et al., 1982; Nagayama et al., 1991; Nierenberg et al., 1995; Jouvent et al., 1998), including the original report on the efficacy of imipramine (Kuhn, 1958), were placebo controlled; thus, it is not possible to conclude definitively that such early improvement was drug-induced. Some studies in which a placebo-treated group of patients was included found early improvement to predict favorable outcome, but both to drug and placebo (Small et al., 1981; Khan et al., 1989). However, a venlafaxine/placebo controlled study (Rudolph et al., 1998) and a meta-analysis of studies involving fluoxetine and placebo (Tollefson and Holman, 1994) revealed significantly greater clinical improvement caused by these drugs with the first two weeks of treatment than that due to placebo. Parker et al. (2000) provided evidence of what he terms a 'trajectory break', i.e. a change in the slope of severity scores vs. time of treatment, in eventual responders to AD treatments. Such data were interpreted to indicate that ongoing early improvement, specifically from day 3 to day 6, is a substantive predictor of responder status. The analysis of Parker et al. (2000) shows the importance of presenting data separately for responders and non-responders, in addition to the total sample, irrespective

of outcome. As stated by Laska and Siegel (1995), not everyone treated with an AD has an onset, i.e. non-responders, and for those who do not, the time to onset has no meaning.

Stassen et al. (1993) presented an important paper with respect to the issue of onset of AD action. They justified the use of a definition of 'onset' as the earliest time when there is a substantial reduction of the total Hamilton Depression (HAM-D) Scale score of at least 20%. Using this approach in conjuction with survival analytic techniques (Kaplan and Meier, 1958; Laska and Siegel, 1995), Stassen et al. (1993) studied 'onset' after treatment with amitriptyline, oxaprotiline or placebo. Active treatments as well as placebo had a median time to onset of about two weeks. In a subsequent meta-analysis using this approach (Stassen et al., 1996), early onset of improvement was highly predictive of later outcome in that 70% of patients showing improvement (i.e. a $\geq$20% decrease in the total HAM-D score) within 14 days became responders. In this analysis, differences between active treatments and placebo emerged within the first five days and reached maximum distinction around day 14. Even more recently, they used this approach (Stassen et al., 1999) in meta-analyses of fluoxetine- and moclobemide-treated patients. For both drugs, onset of improvement in the majority of patients occurred within two weeks and was highly predictive of outcome at six weeks, i.e. over 70% of the early improvers to either drug were responders after five weeks of treatment. This approach, then, has provided no indication for a substantially delayed onset of AD action.

Part of the disagreement about the length of time between the effect of the ADs on the functioning of neurotransmitter systems and clinical response has been in great part a function of the ambiguity of the concept of 'onset of clinical response'. The fact that marked or full response, conventionally defined as equal to or greater than a 50% reduction on the Ham-D total score, can require l.5–3 months to occur is not disputed. If recovery is used as the definition of onset of clinical response, there is no question that a significant lag time exists between it and the initial neurochemical effects of ADs. However, if the onset of clinic response is defined by the type of improvement indicated above by Stassen et al. (1993), rather than recovery, then the average time for the onset of clinical response to ADs is 13 days, significantly less than that required for 'full response.'

Even Stassen et al. (1993, 1997) carried out their analyses using the total Ham-D score, which limits their conclusions to global severity only and does not extend to specific behavioral components of the disorder. One of us (A.F.) has been involved in clinical studies attempting to determine onset of AD efficacy using approaches that quantify separately the behavioral components (i.e. symptoms) of the illness. In an early study (Katz et al., 1987), beneficial clinical effects caused by imipramine in the first 2 weeks of treatment were large and predictive of eventual positive clinical response. This study did not include a placebo control group so questions were asked, appropriately, if the early improvement in treatment responders was due to drug or to a placebo response. Recently, we completed a study that had a placebo group as well as two pharmacologically distinct ADs, desipramine and paroxetine (Katz et al., 2004). The most important finding from that study was that it is possible to detect, within the first week or two of treatment, clinically significant improvement in those depressed patients who eventually respond to pharmacotherapy after a 6-week trial. Furthermore, ADs that target either noradrenergic or serotonergic neurons induced initial improvement on different facets of depressive symptomatology. The selective noradrenergic reuptake inhibitor (NRI), DMI, initiated improvement through effects on depressed mood and motor retardation, with onset of improvement in such behaviors evident within 3–7 days. The (SSRI), paroxetine, on the other hand, produced initial improvement somewhat more slowly and differently than DMI; it improved anxiety by day 10 but not motor retardation or depressed mood. Only later was there improvement in depressed mood, distressed expression, and cognitive functioning (by day 13). In contrast to these consistent and drug-specific early behavioral effects in patients who eventually responded to these drugs, depressed patients who responded to 6 weeks of treatment with placebo showed no consistent early pattern of behavioral improvement. Consistent with these results, Szegedi et al. (2003) found recently that improvement in the first two weeks in depressed patients treated with either mirtazapine or paroxetine was highly predictive of a positive response after six weeks of treatment. Lack of early improvement was also highly predictive of lack of improvement after six weeks. Thus, an increasing body of data is emerging that refutes the concept that ADs initiate behavioral improvement quite slowly, at least not as slowly as widely believed.

Earlier studies may have insufficiently assessed the nature and sequence of specific behavioral changes that might accompany early drug-induced changes in the functioning of the monoamine systems. The difficulty in describing this neurochemical-behavioral process in earlier studies was influenced by the use of 'full clinical response' as the criterion of drug action, rather than treating recovery as a process that begins with changes in parts of the disorder and evolves, sometimes rapidly, into resolution of the full disorder. It is true, though, that some procedures have been reported to produce a more complete antidepressant response much more rapidly than standard antidepressant treatments. Most prominent is the procedure of sleep deprivation, with which 50% improvement in the severity of MDD may be achieved in one day (Kuhs and Tölle, 1991). Unfortunately, the improvement dissipates when the patients go to sleep.

In light of such data, we would suggest that if one purpose of using animal models with predictive validity is to understand the mechanisms by which ADs produce their

clinical efficacy, then one in which ADs begin to produce positive effects in 3–7 days with full effects seen sometime later (e.g. at 3–4 weeks) would be one that more faithfully reproduces the time course of clinical improvement. Given that animal studies often use higher drug doses with concomitantly higher serum concentrations than those used clinically, it is possible that the time course of behavioral improvement described above may be shortened somewhat. Further, it would be useful for such models to distinguish initial effects of SSRIs from selective NRIs, as is the case for the forced swim test (Detke et al., 1995). The recent results of Katz et al. (2004) indicate that although different types of ADs may ultimately achieve the same outcome, i.e. clinical improvement or recovery, they may initially improve different components of the illness.

Such data are consistent with those generated in the innovative work of Delgado and associates (see Delgado and Moreno, 2000), who demonstrated that abruptly reducing the availability of 5-HT through rapid depletion of dietary tryptophan reversed therapeutic efficacy in patients responsive to an SSRI, fluoxetine. When the same procedure was applied to patients responsive to a selective NRI, desipramine, it had no effect. This result occurred in spite of the fact that the depressed patients had been randomly assigned to treatment with either fluoxetine or despiramine (Delgado et al., 1999). By contrast, catecholamine depletion transiently reversed responses produced by selective NRIs without affecting the response to SSRIs. This work reinforces the idea that the neurobiological mechanisms underlying responsiveness to different classes of ADs involve initial actions on different neurotransmitter systems, and that these transmitters are involved in the mechanisms of action of ADs.

2. Behavioral dimensions associated with MDD

Any animal model of depression, or of antidepressant activity, must account for the considerable symptom overlap between MDD and anxiety disorders, e.g. sleep disturbances, agitation, restlessness, irritability; difficulty concentrating, loss of control, fatigue, fear, distress and, of course, anxiety. Indeed, comorbidity of anxiety disorders and MDD is the rule rather than the exception (see Mineka et al., 1998; Lenze et al., 2001; Nemeroff, 2002). Even in the absence of explicit comorbidity, anxiety is a prominent and prevalent symptom of depression (Katz et al., 1984; Gorman, 1997; Fawcett and Barkin, 1998), with as many as 85% of adults with depression having significant symptoms of anxiety (see Gorman, 1997). Further, SSRIs and other antidepressants, such as venlafaxine, are efficacious in many anxiety disorders as well as MDD (see Sareen and Stein, 2000; Brady et al., 2000; Kasper and Resinger, 2001; Brawman-Mintzer, 2001;). All existing antidepressants successfully ameliorate anxiety as a component of depression, including SSRIs, selective NE reuptake blockers (Kleber, 1979; Nystrom and Hallstrom, 1985; Szegedi et al., 1997; Nelson, 1999; Ferguson et al., 2002; Stahl et al., 2002), bupropion (Trivedi et al., 2001) and mirtazapine (Fawcett and Barkin, 1998).

Such observations have led to the development of several theoretical schemata to define the behavioral dimensions that are shared by depression and anxiety disorders (Clark and Watson, 1991; Brown et al., 1998; Mineka et al., 1998; Krueger, 1999). Such formulations may offer a theoretical framework by which to identify neurobiological substrates underlying clusters of symptoms. They may also aid in understanding the regulatory processes by which these component behaviors may be improved through the pharmacologic effects induced by AD drug treatment. One of the most robust of these formulations has been the so-called 'tripartite' model, based on meta-analyses, factor analyses, and measures of convergent and discriminant validity and inter-rater reliability of a number of psychometric instruments, with data derived from both patient and non-patient samples (Clark and Watson, 1991; Mineka et al., 1998; Brown et al., 1998; Watson et al., 1995). In this scheme, three independent factors were derived that account for both the common and unique symptoms and manifestations of MDD and anxiety disorders: Negative Affect, Positive Affect and Physiologic Hyperarousal.

Elements of the *negative affect* dimension were found to be common to both depression and all anxiety disorders, accounting for much of the symptom overlap (see Mineka et al., 1998). This factor resembles other higher order factors, such as 'internalization', 'general distress' or 'neuroticism' that have been described in similar models (see, e.g. Watson et al., 1995; Krueger, 1999). It is defined by negative mood states seen in both MDD and anxiety disorders, and includes symptoms such as agitation, anger, anxiety, fatigue, irritability and hostility. It also includes several cognitive symptoms, such as poor concentration and a sense of loss of control. Some components of Negative Affect, such as sadness, hopelessness, guilt, worthlessness, and suicidal ideation are more prominent in MDD; others, such as fear and helplessness, are associated primarily with anxiety disorders, but many are present in both.

Positive Affect includes feelings of pleasure, joy, energy, arousal, alertness and interest in rewarding activities. It is the lack of Positive Affect, comprising symptoms such as anhedonia, lack of interest in or engagement with the external environment, and psychomotor retardation, that is most closely associated with MDD, and that distinguishes it from anxiety disorders.

The third dimension in this scheme is *Physiologic Hyperarousal*. Symptoms related to this dimension are characterized by autonomic and somatic manifestations such as shortness of breath, lightheadedness, choking or smothering sensations, chest pains or palpitations, nausea, etc. Although somatic symptoms of anxiety may occur in many disorders, physiologic hyperarousal as an independent factor has been most prominently and specifically

associated with panic disorder (Brown et al., 1998; Mineka et al., 1998).

Table 1 ascribes symptoms associated with the diagnosis and classification of MDD and anxiety disorders, as specified in DSM-IV, to the behavioral dimensions defined in the tripartite model. Certain symptoms, such as poor concentration or confusion, describe cognitive, rather than strictly affective components of the illnesses, and it may thus seem counterintuitive to include such symptoms within a factor called 'Negative Affect'. Nonetheless, an attraction of all such models is that they dictate which symptoms cluster together, regardless of subjective similarity. By so doing, they may reveal the dimensional structure that links such disparate behaviors together. Regarding the discussion above, this formulation is consistent with the clinical observation that anxiety, as a component of the Negative Affect dimension, is a key element of both depression and anxiety disorders (see Mineka et al., 1998).

Thus, in attempting to develop animal models to explain the mechanisms of antidepressant efficacy, such dimensional formulations force us to consider how drug-induced regulation of specific neurobiological substrates can account for their effects on the variety of symptoms subsumed within a given dimension. By reducing a myriad of disparate symptoms to a more limited set of dimensions, to which it may be possible to relate the functions of identifiable neurobiological systems, it may thus be more feasible to develop animal models for these behavioral dimensions rather than trying to recreate or mimic the entire spectrum of symptoms comprising the syndrome of depression. The advantage of considering such a dimensional approach from the perspective of animal models is that (1) there are likely to be specific neurobiological systems associated with these dimensions, and (2) it may therefore be possible to test experimentally how antidepressants can induce time-dependent regulatory effects on these systems to influence specific animal behaviors subsumed within these dimensions (e.g. attention, anxiety, reward, etc.) in ways that can be related to their clinical effects.

Table 1

Dimension	Symptom[a]
Negative affect	Sadness
	Worthlessness/Guilt
	Suicidal ideation and behavior
	Sleep disturbances
	Agitation and restlessness
	Irritability
	Poor concentration/distractability
	Loss of control
	Anxiety
	Distress
	Fearfulness
	Helplessness
	Fatigue/Languor
Loss of positive affect	Anhedonia
	Psychomotor retardation
	Hopelessness
Physiologic hyperarousal	Shortness of breath
	Choking or smothering sensations
	Palpitations
	Chest pain/discomfort
	Trembling or shaking
	Sweating
	Nausea
	Dizziness or lightheadedness
	Chills or hot flushes

[a] Adapted from Clark and Watson, 1991; Watson et al., 1995; Mineka et al., 1998; Brown et al., 1998; and reproduced from Morilak and Frazer, in press.

For example, the Negative Affect dimension is comprised of symptoms that fall into two broad categories, those that have an 'activated' component (e.g. agitation, irritability, anxiety) and those that are more 'inhibitory' or withdrawal-like (e.g. sadness, worthlessness, fatigue, languor, helplessness, etc.). Given the relationship that has been demonstrated between tonic noradrenergic activity and attention, alertness, behavioral activation and arousal (Jacobs et al., 1991; Aston-Jones et al., 1991, 2000), it seems likely that the tonic elevation of extracellular NE levels produced by many antidepressants could contribute in some way to the alleviation of many of the inhibitory or withdrawal-related symptoms of both depression and anxiety disorders. Similarly, tonically elevated noradrenergic activity might also improve several symptoms reflecting the deficit of Positive Affect in depression, including psychomotor retardation and a lack of interest or engagement with the external environment.

By contrast, phasic activation of the noradrenergic system facilitates many fear- and anxiety-like behavioral and cognitive components of the acute stress response (Svensson, 1987; Jacobs et al., 1991; Morilak and Jacobs, 1985; Cecchi et al., 2002a,b). Preclinical research has shown that reduction or antagonism of the phasic reactivity of the noradrenergic system attenuates acute anxiety-like behavioral reactivity (Cecchi et al., 2002a,b; Pardon et al., 2002). Thus, whereas elevating tonic noradrenergic activity may improve the withdrawal-like symptoms of depression associated with Negative Affect, it may also be necessary, in order to fully explain the clinical efficacy of antidepressant drug treatment, to hypothesize a concurrent attenuation of phasic noradrenergic reactivity to improve the anxiety-related symptoms of Negative Affect.

As another example, a prominent role for serotonin in the brain appears to be to bias the behavioral repertoire of an organism away from a pattern of activational responses, and to promote instead a pattern of impulse-control and behavioral constraint (Soubrié, 1986; Spoont, 1992; Robbins, 2000). Enhancing such processes, for example by chronic treatment with an SSRI, may thus alleviate symptoms of Negative Affect that reflect a loss of control, excessive reactivity, or impulsivity, including agitation, sleep disturbance, distractibility, fear, anxiety, irritability, anger, hostility, aggression, and suicidal thoughts or acts, accounting for aspects of both the anxiolytic and

antidepressant efficacy of SSRIs. All the hypotheses described in this and the preceding paragraphs, by relating specific behavioral dimensions to the functioning of specific monoaminergic systems, and then postulating specific regulatory alterations induced by chronic antidepressant drug treatment, are clearly amenable to testing in animal models.

In conclusion, we would suggest that it might be profitable to develop animal models that exhibit specific behavioral characteristics reflecting disturbances in, or components of, higher-order behavioral dimensions such as those highlighted above. In so doing, we may then hope eventually to understand not only the neurobiological changes underlying the development or manifestation of symptoms in depression and anxiety disorders, but also the regulatory mechanisms by which antidepressant drugs can alleviate those symptoms.

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