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Review

REVIEW

Relevance of Rodent Models of Depression in Clinical Practice: Can We Overcome the Obstacles in Translational Neuropsychiatry?

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Abstract

The diagnosis of a mental disorder generally depends on clinical observations and phenomenological symptoms reported by the patient. The definition of a given diagnosis is criteria based and relies on the ability to accurately interpret subjective symptoms and complex behavior. This type of diagnosis comprises a challenge to translate to reliable animal models, and these translational uncertainties hamper the development of new treatments. In this review, we will discuss how depressive-like behavior can be induced in rodents, and the relationship between these models and depression in humans. Specifically, we suggest similarities between triggers of depressive-like behavior in animal models and human conditions known to increase the risk of depression, for example exhaustion and bullying. Although we acknowledge the potential problems in comparing animal findings to human conditions, such comparisons are useful for understanding the complexity of depression, and we highlight the need to develop clinical diagnoses and animal models in parallel to overcome translational uncertainties.

Keywords: RDoC, stress, resilience, vulnerability

Introduction

One of the greatest challenges of our society is to prevent and treat mental disorders. Despite major breakthroughs in neuroscience, only limited progress in the treatment of mental disorders has been made in the last 30 years. This can be explained partly by a lack of compatibility between neuroscience and clinical practice.

The diagnosis major depression was introduced in the mid-1970s and incorporated in the third edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) (Spitzer et al., 1978). Since then, the diagnostic system has been improved and advances have been made, including increased awareness of mental health issues and the development of specific forms of psychotherapy. However, the translation between clinical work and animal research is hampered by the fact that the psychiatric diagnostic procedure is open for subjective interpretation of reported symptoms and that it lacks objective measures of behavior or biomarkers. Regarding depression, the collection of disparate symptoms is particularly troublesome (Spitzer et al., 1978). The wide variability of symptoms and clinical presentations among subtypes of depression clearly indicates that depression is not a homogenous disorder but is actually a spectrum of related disorders (Lux and Kendler, 2010).

We argue that animal models are necessary for understanding the neurobiology of the disease. However, it is futile to seek one single animal model for the diagnosis depression. Instead, we should use various animal models, where depressive-like behavior has been induced in different ways, to learn more about

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the mechanisms underlying the psychiatric conditions they model (Table 1). When we compare animal models with clinical conditions, we need to use less well-established clinical descriptions. These conditions are often associated with an increased risk of developing major depression (Figure 1), but are not major depression per se. It becomes clear that the animal models are not diagnostic models, but rather models of risk and vulnerability factors of depression. Importantly, this is not a drawback of the animal models, but again illustrates that the current diagnostic system is neither compatible with neuroscience nor is it sufficient to describe the underlying mechanisms of depression. We will also discuss how these weaknesses can be overcome.

What do we talk about when we talk about depression in rodents?

The translational uncertainties described above, including the lack of functional biomarkers for major depression, complicate the definition of an animal model of depression. Thus, the evaluation of the model needs to be based on clinically relevant symptoms, and these symptoms must be detectable and quantifiable in the animals' behavior. In this text we refer to "tests" as behaviors that can be evaluated, whereas an "animal model" is an animal that has been manipulated as to score higher in these tests.

Table 1. Animal Models of Depression Based on their Mode of Induction as well as Functional Characteristics

Animal Model	References	Induction	Possible Disease Relevance
Stress-Induced			
Chronic mild stress	Katz, 1982; Willner et al., 1987	Unpredictable repeated stress	Studying of risk-factors for burn-out
Unescapable stress	Maier, 1984; Telner and Singhal, 1984	Acute, intense stress	Possible overlapping mechanisms between PTSD and depression
Social defeat	Golden et al., 2011; Krishnan and Nestler, 2011	Forced to subordination	Bullying as riskfactor for depression
Social isolation	Grippo et al., 2007; Djordjevic et al., 2012	Individual housing	
Maternal separation	Matthews and Robbins, 2003; Vetulani, 2013	Maternal separation	Early separation/insecure attachment as riskfactor for depression
Selectivly Bred			
FSL	Gómez-Galán et al., 2013; Overstreet and Wegener, 2013	Sensitivity to cholinergic agents	Tests for antidepressant treatments Vulnerability for stress
Wistar-Kyoto	Paré, 1989; Solberg et al., 2001; Nam et al., 2014	Sensitivity to hypertension	Vulnerability for stress β-blockers effect on behavior
Other selectively bred models		Sensitivity to stress, anxiety, subordination…	Vulnerability factors and risk-behavior associated with depression
Genetic Manipulations			
SERT-KO	Lira et al., 2003	Total knock-out of serotonin transporter	Increased anxiety, serotonergic syndrome,
NET-KO	Haenisch and Bönisch, 2011	Total knock-out of noradrenaline transporter	Protective against depression
BDNF modification	Kaufman et al., 2006	Knock-out of BDNF or TrkB	Study of antidepressant effects
vGlut1-KO	Garcia-Garcia et al., 2009	Total knock-out of vesicular glutamate transporter	Depressive-like behavior Vulnerability to depression
DISC1 KO	Shen et al., 2008	Total knock-out of DISC1	Overlapping symptoms between schizophrenia and depression
Other transgenic animals	Renoir et al., 2013	Specific genetic deletions in targeted organs	Systemic studies on vulnerability to depression
Network Alterations			
Stimulation of raphe nucleus	Warden et al., 2012	Optogenetic activation of PFC projections to Raphe Nucleus	The role of serotonin in depression
Inhibition of VTA	Tye et al., 2013	Optogenetic inhibition of VTA projections to Nucleus Accumbens	The role of dopamine in depression Neuronal activity pattern as vulnerability to depression
D2 receptors in basal ganglia	Francis et al., 2014 Dias et al., 2014	Targeted modification of D2-containing neurons in the striatum	Dopamine pharmacology to treat depression Striatal microcircuit involvement in depression
Stimulaion of central amygdala	Tye et al., 2011	Optgenetic activation of central nucleus of amygdala	Protective against development of depression
Stimulation of Hanbenula	Hsu and Wang, 2014	Optogenetic activation of habenula	Reinforcement and aversion in depression
Neuroinflammation			
LPS injection	Yirmiya, 1996	Stimulation of inflammation	Relationship inflammation - depression
Injections of IL6, IL1 or kynurenine	Fleshner et al., 1995; Smagin et al., 1996	Stimulation of specific inflammatory pathways	Relationship inflammation – depression Systemic signals involved in depression

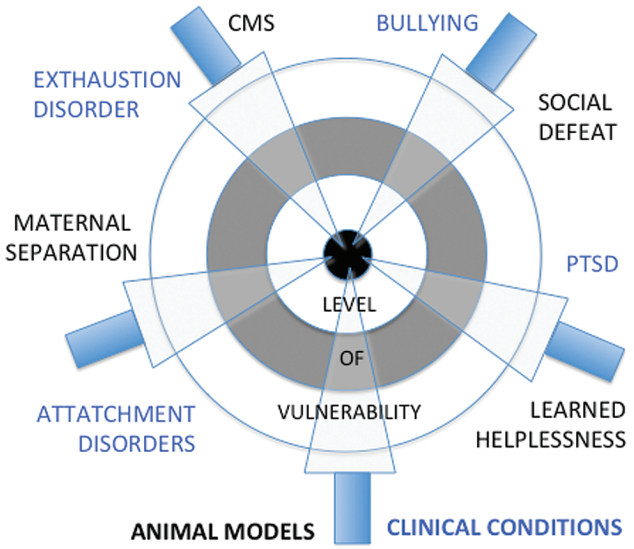

Figure 1. Scheme of exposures (arrows) and vulnerabilities (circles) that increase risk of depression. By combining risk factors for depression identified in the clinic with specific neurobiological manipulations in animal models, we will achieve a better understanding of the pathophysiology of depression.

The best established and most commonly used tests for depressive-like behavior in animals have been developed for predictive value; that is, an animal's response to a given treatment can predict if the treatment will have an antidepressant effect in humans. The Porsolt swim test (Porsolt et al., 1977) and the tail suspension test (Cryan et al., 2005) measure an animal's struggle to escape an unpleasant situation (i.e., being in water or hanging upside-down, respectively), and these tests are commonly used by the pharmaceutical industry to predict how patients will respond to a given antidepressant drug. It can be argued that these tests also have face value, as a decreased struggle can be interpreted as a lack of motivation or despair—behaviors that are common among patients with depression.

Another commonly used test for depression is to measure anhedonia (a loss of the ability to derive pleasure from an activity that usually produces pleasure) by comparing how much an animal prefers sweetened water to unsweetened water. A lost preference for sweet water is interpreted as anhedonia, a depressive symptom (Willner et al., 1987). To avoid any possible bias due to metabolic factors, anhedonia can be tested more directly using a self-stimulating paradigm where a stimulating electrode is implanted in a brain area mediating reward. The animal can then self-stimulate by pressing a lever or poking its nose into a hole; a decreased propensity to self-stimulate is considered to reflect anhedonia (Vogel et al., 1986).

A newly developed test is aiming for another core symptom in depression: negative bias. In this test the propensity for a rat to choose a reward rather than to avoid something unpleasant is measured (Hales et al., 2014). Other tests that are gaining in popularity are based on natural behaviors, such as social interaction and/or the motivation to explore, rather than examining the response to a given stimulus or stressful situation. For example, our group and others have shown that decreased exploratory behavior is associated with a depression-like phenotype (Kasahara et al., 2007; Li et al., 2010; Gómez-Galán et al., 2013; Magara et al., 2015). Several auxiliary tests can be used to obtain a more complete evaluation of an animal model or the response to a drug; in particular, tests for memory and anxiety are commonly used (Lapiz-Bluhm et al., 2008).

Stress-Induced Models of Depression

In humans, depression can occur in the absence of any notable life stressor, while conversely many individuals who are exposed to chronic life stressors never develop clinical depression (Feder et al., 2009). Nevertheless, many patients with depression often describe stress-inducing life events as contributing factors, and stress is commonly used to induce depressive-like behavior in animals (Slattery and Cryan, 2017). Studies using these stress-induced models of depression have generally reported an increase of plasma corticosterone, and the depressive-like behavior is not elicited when the stress response is reduced (such as in adrenalectomized or genetically modified animals; Keeney et al., 2006; Goshen et al., 2008). Likewise, major depressive disorder has been associated with increased production of corticotropin-releasing hormone and cortisol as well as increased size of the pituitary and the adrenals, indicating a general increased activity of the hypothalamic–pituitary–adrenal axis (Dinan, 1994) together with possible glucocorticoid receptor resistance and defective negative feedback (Pariante, 2004).

Chronic Stress

The most common model, and one of the best-validated, is the chronic mild stress model (Katz, 1982; Willner et al., 1987) in which animals are subjected to stressors several times a day at unpredictable time points. This protocol minimizes the impact of acute stress, as each intervention (loud noise, tilting of the cage, wet bedding, etc.) causes only moderate stress. One major advantage of the chronic mild stress model is long-lasting effects allowing investigation of long-term administration of antidepressant drugs. Although this model has a reputation of being unreliable, a recent survey suggested that the unreliability may not be worse in this model compared with other depression models (Willner, 2017).

By design, the chronic mild stress model could be viewed as resembling exhaustion disorder, in humans caused by difficulties in coping with life and occupational stress. Exhaustion disorder is characterized by a long prodromal phase that can include reduced energy and increased emotional instability, eventually progressing to an acute phase that includes exhaustion, hopelessness, and apathy. Recent studies suggest that exhaustion disorder is separate from anxiety and major depression (Besèr et al., 2014), whereas others report considerable comorbidity between exhaustion disorder and major depression (Glise et al., 2012). This may indicate either that exhaustion corresponds to one aspect of depression or that exhaustion increases the risk of depression. Regardless of the interpretation, the chronic mild stress animal model is an important tool for understanding the relationship between depressive-like behavior and sustained, unpredictable stress.

Acute Stress

Another well-characterized model of depression displaying a wide variety of depressive-like behavior is the learned helplessness model. This model is based on repeated exposure to an inescapable acute threat, such as a foot-shock or a pinch to

the tail in a box where the animal learns that it has nowhere to escape (Maier, 1984; Telner and Singhal, 1984). Social defeat can be considered a variant of the learned helplessness model, where the stressor is chosen to be innate to the rodent, namely subordination to a dominant peer (Golden et al., 2011; Krishnan and Nestler, 2011). Typically, animals are put as intruders in the home cage of a large dominant male and thus forced to subordination.

In addition to being well characterized models for depression, the learned helplessness model, as well as the social defeat model, produce physiologic and behavioral symptoms that models aspects of PTSD (Pulliam, 2010; Schöner, 2017). The exposure to an inescapable acute threat, as in the learned helplessness model, corresponds to the first DSM criterion for posttraumatic stress disorder (PTSD). Interestingly, situations of power imbalance such as workplace bullying, often including sexual harassment, are also associated with an increased risk of development of PTSD (Spence Laschinger and Nosko, 2015) as well as depression (Lund et al., 2009). Moreover, patients exposed to trauma or stressful events often exhibit anhedonia and dysphoric symptoms (among others) rather than anxiety- or fear-based symptoms. The learned helplessness and social defeat models may thus be useful tools to study how different types of acute, severe stress affects the risk of acquiring depressive-like behavior.

Social Stress

Another way to use social stress in animal models is social isolation. Individual housing for 4 weeks has been shown to induce depressive-like behavior (Grippo et al., 2007; Djordjevic et al., 2012). A specific form of social isolation is maternal separation, another commonly used model of depression (Matthews and Robbins, 2003; Vetulani, 2013). In this model, the lactating dam is taken out of the cage for about 3 hours every day from the second to the twelfth day postpartum. This treatment is complex and goes beyond pure isolation (Lehmann and Feldon, 2000), and it leads to depressive-like behavior that persists into adulthood. This agrees with the fact that childhood separation and parental neglect can lead to long-lasting attachment insecurity in humans (Waters et al., 2000). Both attachment insecurity and early separation have been associated with depression (Roberts et al., 1996; Otowa et al., 2014), and emotional dysregulation has been proposed as the link between these triggering events and depression (Malik et al., 2015).

Vulnerability to Stress

In addition to these commonly used models of stress-induced depression, many other paradigms of stress have been used. Nevertheless, we still lack a comprehensive picture of how different depression-triggering mechanisms are induced by different modalities of stress, or differences in when, and for how long, stress is applied. Comparing different stress-induced models will help us to get a clearer picture of the differential effect of different types of stress and its timing. Experimental animal models can also be studied to identify factors of vulnerability and resilience to different types of stressors (Dias et al., 2014). Vulnerability factors and environment may interact to produce depression, as has been shown for a specific serotonin transporter allele that renders an individual more sensitive or less sensitive to stressful life events (Caspi et al., 2010; Wang et al., 2011).

Neurobiological Models of Depression

Selectively Bred Animal Models

Selectively bred animal models are used to study depression, with the 2 most commonly used being the Flinders sensitive line (FSL) and the Wistar-Kyoto line. The FSL rat was selectively bred for sensitivity to acetylcholinesterase inhibitors (Overstreet et al., 1986) and displays several depressive-like behaviors, including increased immobility time in the Porsolt's swim test, decreased cognition, and increased anxiety (Gómez-Galán et al., 2013; Overstreet and Wegener, 2013). Thus, one could hypothesize that an increased sensitivity in the acetylcholine system is associated with depressive-like symptoms, although FSL rats also have deficiencies in many other systems, including dopaminergic and glutamatergic transmission (Overstreet and Wegener, 2013).

The Wistar-Kyoto line was developed as a control group for hypertensive rats and was subsequently found to have increased stress responses, altered sleep patterns, and depressive-like behavior in the Porsolt's swim test (Paré, 1989; Solberg et al., 2001; Nam et al., 2014). These rats have a mixed response to antidepressants and have been selectively bred further to establish lines of "more immobility" and "less immobility," which respond differently to antidepressants (Will et al., 2003; Andrus et al., 2012).

Although we still do not understand the underlying mechanisms of depressive-like behavior in the FSL and Wistar-Kyoto lines, the transmitter systems used for selection in the development of these two lines are paralleled with observations in human depression. Cholinergic signaling, which was the target system in the development of the FSL rat, regulates social stress, anxiety, and depressive-like behavior (Mineur et al., 2013). The adrenergic system, which regulates blood pressure and was targeted in the development of the Wistar-Kyoto rats, has not been primarily associated with depression, and results obtained from clinical trials using antihypertensive drugs vary. Although ß-blockers, and propranolol in particular, have been found to be associated with depression, it has been argued that the behavioral changes associated with propranolol do not resemble classic depressive syndrome (Patten and Barbui, 2004).

In addition to the well-characterized FSL and Wistar-Kyoto lines, several groups have bred animals selecting for a specific depression-like behavior. In addition to the behaviors that they were selected on, these animals show disturbed sleep pattern, increased plasma corticosterone, and reduced levels of baseline serotonin and brain-derived neurotrophic factor (BDNF) (El Yacoubi et al., 2003; Will et al., 2003; Gersner et al., 2014).

Selectively bred models can focus on one particular behavior among the depressive-like symptoms, thus allowing study of the neurobiology or potential treatment of that particular construct. In contrast to models where selection is based on a known mechanism, models based on a specific behavior allow us to discover unexpected mechanisms of relevance to depression. The drawback of the unknown etiology is that it does not allow us to draw causative conclusions.

Genetic Models

Twin studies suggest that the genetic contribution to depression ranges from 10% to 50% (Silberg et al., 1990; Edvardsen et al., 2009), and several genes have been associated with depression;

however, no gene has emerged as the main gene underlying the disorder (Flint and Kendler, 2014). The lack of conclusive genetics data in animal models and human patients can have two possible explanations: either depression is a highly complex trait, or depression is not actually one disease but rather a disease spectrum that can be induced by a wide variety of biological causes (Andrus et al., 2012; Gómez-Galán et al., 2016).

Nevertheless, attempts have been made to use genetic modifications in mice to study depression, and the serotonergic and noradrenergic systems have provided obvious targets for such modifications. Interestingly, genetic deletions of the norepinephrine transporter are protective against depression induced by restrained stress or social defeat (Haenisch and Bönisch, 2011), whereas deleting the serotonin transporter leads to a phenotype that resembles the acute effect of selective serotonin reuptake inhibitor treatment, including increased anxiety or even serotonergic syndrome (Lira et al., 2003). Genetic downregulation of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis, increases depressive-like behavior (Savelieva et al., 2008).

A single nucleotide polymorphism in the human BDNF gene increases vulnerability to stress-induced depression (Kaufman et al., 2006), making this gene a target for depression models. However, when BDNF function is reduced through genetic modification of BDNF or its receptor TrkB, no unequivocal link to depression is found. Instead, reduced BDNF function leads to cognitive impairment and obesity (Lindholm and Castrén, 2014).

Recent work describes depression as a misregulated glutamate transmission or an unbalance in excitation and inhibition, leading to studies targeting genes involved in the regulation of glutamate. For example, reduced levels of the vesicular glutamate transporter lead to increased depressive-like behavior and increased vulnerability to stressors (Garcia-Garcia et al., 2009).

In contrast to selectively bred animals, a model that has been modified with targeted genetic manipulation could allow to establish a causative link between a biological function and the depressive-like behavior. However, it is important to note that the specificity of a genetic mutation can be deceiving. A genetic change will affect many compensatory and downstream pathways, and the most relevant mechanism may be hard to pinpoint. In addition, many pathways converge on the same behavior; for example, the 4 distinct genetic models targeting serotonin, glucocorticoid, glutamate, and cannabinoid signaling were all recently reported to share the behavioral changes (Hoyle et al., 2011). For an extensive review of targeted genetic modifications that lead to depressive-like behavior, see (Renoir et al., 2013).

Animal Models with Specific Network Alterations

The development of targeted genetic manipulations and optogenetics, where a light-activated ion-channel can be selectively inserted and activated in a population of neurons, has made it possible to study specific circuits and/or signaling pathways in behavioral dimensions relevant to depression (Berton et al., 2012; Deisseroth, 2014). For example, stimulation of the raphe nucleus through direct activation of projection neurons in the prefrontal cortex reduces immobility in the forced swim test (Warden et al., 2012) as does inhibition of NMDA receptors in prefrontal projections to the thalamus (Miller et al., 2017). In addition, activating or inhibiting the dopaminergic neurons in the ventral tegmental area–nucleus accumbens connection can reduce or increase depressive-like behavior, respectivly (Tye et al., 2013), and phasic firing of these projections increases susceptibility to social stress (Chaudhury et al., 2013). Stimulating the dopamine D_1-receptor expressing neurons in the basal ganglia increases the resilience to developing depressive-like behavior, whereas activating the D_2-receptor expressing neurons increases the vulnerability (Francis et al., 2015), suggesting a differential role of these two populations in mediating resilience to depressive-like behavior. Moreover, overexpressing of the signaling molecule β-catenin in D_2-expressing neurons only specifically increases resilience to the social defeat protocol (Dias et al., 2014). Finally, stimulating the central nucleus of the amygdala reduces anxiety-like behavior (Tye et al., 2011), whereas specific molecular manipulations have revealed that the habenula regulates reinforcement and aversion (Hsu and Wang, 2014) that can explain part of the depressive-like behavior (Hsu et al., 2016).

These experiments using specific genetic manipulations have been extremely fruitful in terms of elucidating the neurobiological mechanisms that underlie various dimensions of depressive-like behavior. Together with refined imaging in animals as well as humans, we will get an increased understanding of how a specific neuronal population or network can be involved in the pathophysiology of depression (Chen et al., 2017), and they provide valuable information that can be used to predict the clinical response to pharmacotherapy (Haenisch and Bönisch, 2011). However, it is striking to note how different manipulations in different areas of the brain can induce a similar phenotype. This may be interpreted either as overlapping systems or that brain circuits interact: disrupting any one of them trigger similar pathology. Thus, in addition to identifying the pieces of the puzzle, we must also assemble these pieces correctly to form a coherent picture.

Neuroinflammation

There is a well-established link between inflammation and depression (Krishnadas and Cavanagh, 2012), and injection of the inflammation-inducing agent lipopolysaccharide (LPS) is a popular model for inducing depression (Yirmiya, 1996). Specific pathways in the inflammatory response have also been targeted to study the mechanisms of inflammation-induced depression, including IL-6, IL-1, and kynurenine. The injection of proinflammatory cytokines activates the hypothalamic–pituitary–adrenal axis as seen through increased cortisol levels, depletion of hypothalamic noradrenaline, and increased extracellular levels of noradrenaline (Fleshner et al., 1995; Smagin et al., 1996). Activation of inflammatory pathways is, however, not enough, since cytokine-induced depressive-like behavior was abolished in the serotonin transporter knock-out mice; this implies the involvement of the serotonin modulatory system (van Heesch et al., 2013). In addition to soluble signaling molecules, the vagus nerve plays a major role in the communication between the peripheral inflammatory response and the brain, and vagotomy protects from IL-1 and LPS-induced depressive behavior (Konsman et al., 2000).

In humans, depression has been associated with increased serum levels of the proinflammatory cytokines IL-1β, IL-6, and TNFα (Howren et al., 2009; Dowlati et al., 2010). Furthermore, during severe infections and inflammatory diseases, patients often show a typical sickness behavior defined by lack of energy, apathy, lack of interest, reduced intake of food, etc., thus closely resembling major depression (Dantzer et al., 2008). Recent

work reveals tryptophan catabolism as a converging point for immunological factors and neurotransmission. The conversion of L-tryptophan to N-formyl-kynurenine is governed by the rate-limiting IDO/TDO enzyme (Rafice et al., 2009). IDO is modulated during immune responses (Babcock and Carlin, 2000), and major depression has been associated with increased levels of the tryptophan metabolite quinolinic acid in the cerebrospinal fluid (Bay-Richter et al., 2015).

Overall, there is ample evidence from both animals and humans that inflammatory pathways are involved in depression. Evaluation of their cross-talk is an important field of future work (Feder et al., 2009).

Discussion

We have reviewed animal models used in depression research, based on how the depressive-like behavior is induced. We argue that it is impossible to find one valid animal model of depression that reflects all the aspects of the disease; rather, different animal models should be used to study different aspects of depression. Experimental models offer the opportunity to expose the animals to one factor at a time, thus allowing us to study vulnerability factors and objectively measure and quantify proposed mechanisms involved in depression. A critical step to develop better treatment and prevention of depression is now to improve the understanding between clinical practitioners and basic researchers through the development of a common context for depression. In our point of view, such a context must involve symptoms (regardless of whether these fulfill all the necessary criteria for major depressive disorder according to the DSM or not) as well as etiologic factors, exposure, and vulnerabilities.

To enhance the interaction between clinic and neurobiology, the NIMH has proposed to use Research Domain Criteria (RDoC) as a novel approach to categorizing psychiatric conditions (see http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml). The intention is to create a system based on well-defined constructs (e.g., response to threat, responsiveness to reward, long-term memory within the larger domains: negative valence system, positive valence system, cognition, social response, and arousal) that will facilitate communication between research and clinic. At their homepage, the NIHM describes RDoC as "a framework to guide classification of patients for research studies, not as an immediately useful clinical tool." However, as discouraging as this may sound to any clinical psychiatrist, we argue that such a common context can be achieved without dramatic paradigmatic shifts in the clinic.

The current diagnostic criteria for major depression do not emphasize how core symptoms of depression like anhedonia, motor retardation, and despair have developed. However, it is only when the reported symptoms are combined with a thorough analysis of exposures to risk factors and vulnerability factors that the clinical picture emerges. Identification of the relevant constructs of RDoC overlaps with the taking of such a clinical history (Table 2) and will be directly relevant for the diagnosis.

From a clinical point of view, RDoC could be used to improve the diagnostic specificity and specificity of treatment by increasing the theoretical ground on which the clinical decisions are based. RDoC may thus guide the clinician to more information from the relevant animal models. For example, if the clinical picture is dominated by the construct "response to threat" of the negative valence domain, the clinician may find more information from the corresponding animal models of social defeat and learned helplessness, and if the clinical picture involves the construct "disrupted attachment" of the social processes domain, the clinician may gather more information from the corresponding animal model of maternal separation rather than without further notice giving the patient a major depressive disorder diagnosis.

From a neuroscience perspective, a common context of depression, where clinicians put more emphasis on risk factors and vulnerability factors specified as constructs of RDoC, would lead to a stronger validation of the animal models, generate more specific hypothesis, and enhance development of more specific drugs and better tools to uncover the neurobiology behind symptoms (Figure 2).

In summary, the gap between the clinical practice and neuroscience may be smaller than initially thought, and the use of RDoC may indeed be a way to bridge this gap. Clinical experience is necessary to develop fruitful animal models, but the animal models are also needed to delineate the complex patterns of different exposures and vulnerability factors characterizing the clinical situation, indicating the potential mutual benefit between research and clinic (Figure 2). RDoC may facilitate these iterations. If constructs are studied in patients and in animal models, this will shorten the length of the iteration cycle and facilitate early identification of potential breakthroughs or

Table 2. Research Domain Criteria as Risk Factors for Depression, Their Clinical Manifestations, and the Coresponding Animal Behavior

Domain	Constructs	Clinical Manifestations	Experimental Animal Tests
Negative valence	Acute threat	Powerlessness	Lack of social interaction Porsolt swim test
	Sustained threat	Exhaustion, powerlessness	Porsolt swim test Lack of social interaction
	Frustrative non-reward	Exhaustion	Lack social interaction
	Responses to potential harm	Anxiety	Elevated plus maze, Open field, Novelty suppressed feeding
Positive valence	Reward valuation	Anhedonia	Sucrose preference, self stimulation
Arousal	Arousal, interaction with valence	Appetite, sleep, sex, locomotors activity	Sleep-pattern, social interaction, modified serial-5 choice
Social processes	Disrupted attachment	Disorganized attachment	Aggressive behavior
	Disrupted affiliation	Victimization Social withdrawal	Subordination, Social withdrawal

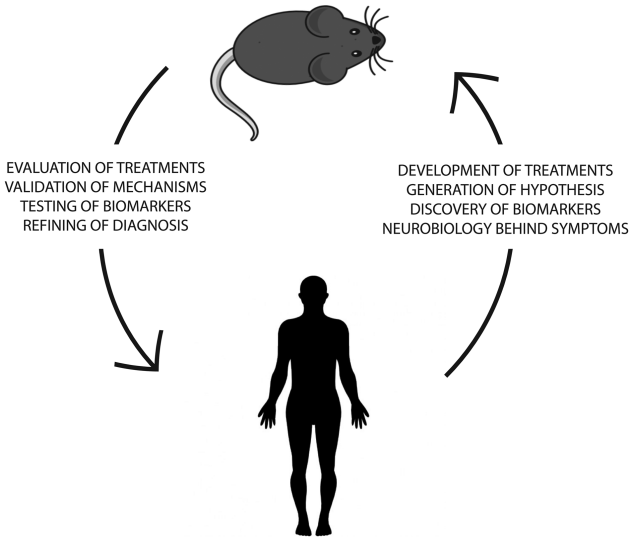

Figure 2. To be able to study relevant mechanism of depression, we need to find a common context for clinical and experimental work. For most, if not all, diseases it will be impossible to generate animal models that can serve as faithful models of a specific diagnosis that could be used to test treatments. Instead, animal models should be seen as experimental tools where hypothesis regarding biological correlations or mechanisms can be investigated and where new hypothesis regarding the clinical condition can be tested. It is only by combining findings from the clinical and experimental fields that we will achieve better diagnosis and treatment.

dead-ends. Furthermore, the different animal models of depression, elucidating different aspects of depression, may be used to refine these constructs and make them even more relevant for the clinic.

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Statement of Interest

None.

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