Animal models of major depressive disorder and the implications for drug discovery and development

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Abstract

Depression is a highly debilitating syndrome that affects the global population and is associated with disabilities and suicide. Depression remains poorly studied and is often treatment resistant and recurrent. Thus, development of new therapies and drugs is needed in the field. Animal models are indispensable for translational biological psychiatry, and may advance the study of depression. While poor understating of psychiatric disorders (including depression) is slowing down further progress in the field, novel approaches continuously emerge that may help untangle disorder heterogeneity and blurred categories of contemporary diseases classification systems. Dividing core symptoms into easily translatable phenotypes is an effective way to reevaluate current paradigms. Also, other, more deep and complicated approaches and theories based on the endophenotype paradigm, such as ‘cross-species trait genetic’ and ‘domain interplay concept’ do continuously emerge to improve current paradigms and drug screening.

Keywords: depression, major depressive disorder, animal modeling, depression theories, depression pathogenesis, endophenotype
1. Introduction

With over 300 million affected people globally, major depression is the largest cause of human disability\(^1\). Depression is a highly heterogeneous clinical disorder the diagnosis of which is complicated due to broad phenomenological criteria and poorly understood neurobiological bases\(^2\text{-}^5\). Associated with mood-, appetite-, sleep-, energy-, cognitive-, motor- and other deficits, depression symptoms may be grouped into several distinct neuropathological subtypes\(^2\)(Table 1). Thus, clinical or preclinical modeling of depression is complicated by the fact that we deal with multiple ‘depressions’\(^6\text{-}^8\).

Another problem is that approximately 1/3 of depressed patients are treatment-resistant, and the disorder has high rates of recurrence\(^9\text{-}^{13}\) and comorbidity with other brain illnesses\(^14\text{-}^{15}\) (Fig. 1). Furthermore, most existing antidepressant drugs have slow-onset action (weeks or months), and other available therapies, such as electro-convulsive therapies have significant side-effects (e.g., amnesia)\(^5\). Thus, development of new therapeutic methods and antidepressants that address these limitations are desperately needed in the field\(^5\text{-}^6\). However, this becomes a particularly challenging task, given the lack of pathophysiological understanding of this disease. Indeed, the most widely accepted monoamine imbalance hypotheses\(^17\text{-}^{18}\) cannot account for limitations discussed above (delayed effects, treatment resistance), and recently proposed ‘inflammation’ hypotheses\(^19\text{-}^{21}\) do not account for major neurotransmitter deficits common for depression. Thus, further progress is urgently needed in the field, including conceptually new, paradigm-shift approaches and theories\(^16\text{-}^{22}\text{-}^{23}\).

Animal (experimental) models are an indispensable tool in translational and neuroscience research\(^23\text{-}^{24}\), relying on several well-recognized validity criteria, such as face (similarity of phenotypes), construct (similarity of neurobiological mechanisms) and predictive (similarity of treatment responsivity) validity\(^10\text{-}^{25}\text{-}^{27}\). For clear ethical, practical and historical reasons, most research utilizes rodents to study depression and other affective disorders\(^10\text{-}^{28}\text{-}^{34}\) (Fig. 2). Rodent models of depression are relatively well-established, and target different aspects of depression (Table 2), including stress\(^35\text{-}^{40}\), genetics\(^41\text{-}^{49}\), inflammation\(^50\text{-}^{53}\) and drug responses\(^54\text{-}^{56}\). Here, we
recognize multiple challenges currently faced by the field of experimental depression models. The present report is a multi-lab effort, lead by the International Stress and Behavior Society (ISBS) Special Panel on experimental and translational depression models.

Many animal models of depression display homologous physiological and neurochemical responses. For example, stress-based models, such as chronic unpredictable stress, chronic social defeat stress, chronic restraint, prolonged social isolation and single prolonged stress, not only result in depression and anxiety-like behavioral phenotypes, as well as memory and sleep disturbances, but also increase plasma models of molecular biomarkers (e.g., interleukins IL-1β, IL-6, TNF-α) and decrease neurotrophins (e.g., BDNF and NGF) in the brain – the effects which can be reversed by antidepressant treatment\textsuperscript{23, 35-40, 57-64}. Since stress is the most common factor of depression onset and progression\textsuperscript{26, 57}, high face and construct validity, predictive power and relative simplicity make stress-based models widely used to model depression\textsuperscript{23, 65}.

While genetic vulnerability plays a role in 35–40\% of variance in depression\textsuperscript{66}, human genetic analyses often fail to identify reproducible genetic loci that contribute significantly to depression\textsuperscript{67}. Indeed, reflecting the multi-factorial nature of depression, recent genetic studies reveal deep connections between psychiatric disorders, including depression, and immune factors, neuronal signaling, synaptic density and histone cascades, suggesting the presence of larger risk clusters in these pathways\textsuperscript{68}. Genetic rodent models indicate the role of serotonergic\textsuperscript{41-44}, noradrenergic\textsuperscript{45-46, 69-70}, dopaminergic\textsuperscript{71-72}, opioid\textsuperscript{73-74}, GABA-ergic\textsuperscript{10, 75-76} and glutamatergic\textsuperscript{77-80} systems in depression-like behavior. However, translation of these models into human depression faces difficulties due to restriction of knockouts to one gene and, at the same time, simultaneous involvement of most core neurotransmitter systems in animal depression-associated behavior. Moreover, depression is also recognized as a result of gene \texttimes{} environment interactions (GxE), acting as a susceptibility and a trigger, respectively\textsuperscript{81-82}.

There are also other behavioral paradigms that are tightly related to depression-like behavior. For example, sickness behavior (Table 2) is associated with depressive behavior and usually evolves as acute sickness reaction to an inflammatory agent, followed by gradually
increasing depression-like behavior, including social withdrawal and motor retardation. This effect involves cytokine signaling pathways and can be induced by a wide range of agents, including polysaccharide (LPS), viral mimic polyriboinosinic-polyribocytidylic acid (Poly I:C), interferon (IFN)-α, bacillus Calmette-Guerin (BCG). Some overlaps between drug withdrawal and depression also exist and have been reported in rodents for cocaine, amphetamine, ethanol, morphine and nicotine (also note hypomania following antidepressant discontinuation both in clinical practice and animal models).

Now that there are good models of inducing depression in animals, the next logical question is whether we have reliable methods to assess animal depression-like behaviors? This question is also important because antidepressant drug discovery heavily relies on such tests. The core depression-related symptoms that can be accessed in rodents include anhedonia, eating and sleep disturbances, agitation or retardation of motor activity, cognitive deficits, energy loss, despair as well as neuroimmune and neuroendocrine disturbances. However, these symptoms are not specific to depression, and can often occur in other psychiatric and other diseases. For example, the forced swim test (FST) and the tail suspension test (TST) are commonly used to access behavioral despair in rodents. However, albeit considered one of the main depression-like states, despair is not unique for depression and can be observed in other models. Thus, a wider range of tests and/or complex batteries of behavioral tests that address distinct domains should be used to increase rates of successful antidepressant drugs determination.

2. Non-rodent models of depression

While rodent depression-like states and effects of antidepressants have long been recognized, many other model species exist that can be used to target evolutionarily conserved depression-related states. For example, non-human primates can bridge a gap between rodent and human models, whereas zebrafish models can provide novel complementary data (in addition to rodent models) that may untangle high heterogeneity of depression by focusing on its core, evolutionarily conserved roots (Table 3). Common models of depression in non-human primates involve maternal or social separation and reflect various aspects of human...
depression such as despair, anhedonia and lethargy. Such models are validated pharmacologically, and, interestingly, antidepressants seem to have similar time course to that observed clinically (unlike in some rodent models). Other drugs, including amphetamine and ethanol, exert antidepressant effects in non-human primates, whereas g-methyl-p-tyrosine or reserpine reduce social interactions and locomotion, as well as induce anhedonia-like lack of environmental interaction. Interestingly, depressive behaviors can occur in macaques spontaneously, strikingly reproducing human depression. Likewise, neurochemical alterations in primate oxytocin, monoamines and their metabolites also resemble alterations observed in depressed patients. Finally, non-human primates are also used to model depressive behavior in chronic stress and cytokine-induced depression.

Among lower vertebrates, zebrafish represent an interesting model organism to study complex CNS states, including anxiety, addiction, autism, obsessive-compulsive states and depression. Similarly to rodents, zebrafish depression-like states can be induced using stress, genetic or pharmacological manipulations (Table 3). For instance, zebrafish chronic stress exposure elevates anxiety-related behavior, increases whole-body cortisol, IL-1β, IL-6, adenosine, mr, gra, grβ, bdnf in telencephalon, CRH, calcineurine, pCREB levels in brain, alters dendritic spines, reduces weight, and lowers dopamine and 5-HIAA levels. Importantly, many of these effects can be corrected by antidepressant treatment, thereby showing highly homologous chronic stress responses to those observed in rodents and humans. Moreover, zebrafish depression models differ from those in mammals (e.g., bdnf/BDNF expression is often reduced in human and rodent depression models), therefore providing not a “smaller mouse” model, but a truly complementary tool to study specific aspects of depression pathogenesis in-vivo.

While zebrafish possess some features that may cumulatively surpass advantages those of rodents, its use in biological psychiatry is still developing, and therefore meets obstacles, challenges and skepticism. For example, it is still unclear how to properly distinguish zebrafish anxiety-like and depression-like phenotypes (if they are distinct at all), thus necessitating further
deep phenotyping and developing of tests that can access more precisely various features of
experimental depression.

3. Theories of depression pathogenesis and new trends

From 1948, when serotonin was first isolated, purified and identified as a monoamine\textsuperscript{155-156}, and 1969, when it was first linked to depression\textsuperscript{155}, the field has clearly moved a long way. For example, there is a great diversity of serotonin receptors that can produce different effects depending on neuron type and cellular localization. Since 5-HT\textsubscript{1A} agonists exert anxiolytic and antidepressant properties, it has been hypothesized that this type of receptor plays a role in developing depression. Postnatal antidepressant treatment can result in anhedonia, anxiety, increased (learned?) helplessness and other depression-related disturbances in adult rodents\textsuperscript{113, 157-158}, whereas 5-HT\textsubscript{1A} knockout in mice display antidepressant-like behavior\textsuperscript{29, 159-160} and serotonin transporter knockout rodents display anxiety-like and higher stress vulnerability\textsuperscript{41-44}.

Another hypothesis of depression is based upon inflammation caused by stress, as the expression of IL-1\beta, IL-6, TNF-\alpha and IFN-\gamma genes were significantly higher in patients with major depression\textsuperscript{161-162}. Furthermore, elevated stress hormones can impact the expression of several neurotrophic factors, thus influencing on neuroplasticity, which is impaired in depressed patients\textsuperscript{161}. Likewise, the hypothalamic–pituitary–adrenal (HPA) axis function is altered in depressed patients as well as in depressed rodent models, and reversed by antidepressant treatment\textsuperscript{161}. Likewise, disturbances of affective spectrum can occur after exposure to inflammatory agents (e.g., lipopolysaccharide (LPS)\textsuperscript{83-86}, viral mimetic polyriboinosinopolyribocytidylic acid\textsuperscript{90} and some autoantibodies\textsuperscript{163}) or as a result of genetic manipulations of pro/anti-inflammation-related genes (e.g., \textit{IL-10}\textsuperscript{51-53} and \textit{TNF-\alpha} knockout models\textsuperscript{50}). In line with this, anti-inflammatory agents can reduce depressive symptoms in humans\textsuperscript{164} and animals. For example, an anti-inflammatory microglia inhibitor antibiotic minocycline prevents LPS-induced increase in cytokines expression and indoleamine 2,3 dioxygenase (IDO, the tryptophan-degrading enzyme), blocking both sickness- and depression-like behavior in mice\textsuperscript{165}. Interestingly, IDO antagonist 1-methyl-D,L- tryptophan exposure does not alter LPS- and Bacillus Calmette-Guerin
(BCG)-induced proinflammatory cytokines and sickness-like, but reduces depression-like behavior\textsuperscript{95, 165}, suggesting that novel anti-inflammatory agents can be screened for further use in depression treatment.

Aberrant GABA neurotransmission has also been linked to depression, as major depression is associated with GABRA1, GABRA5, GABRA6 and GABRG2 genes, and childhood mood disorders - with a male-specific polymorphism of the GABRD gene\textsuperscript{161}. Consistent with this, major depression is generally accompanied by reduced GABA levels, which can be restored by conventional antidepressant treatments\textsuperscript{161}. Interestingly, genetic modifications of GABA-associated proteins may affect anxiety and depression in different ways, since the glutamate decarboxylase (GAD65) knockout and GABA-B1 knockout display high anxiety-like but lower depression-like behaviors\textsuperscript{10, 75-76}, thereby providing a potentially valuable tool to dissect these two commonly comorbid (and frequently overlapping) conditions.

The reduction in astrocyte function and increased microglial activity and related markers are key features of major depression\textsuperscript{166-168}. Indeed, astrocytes are crucial to neuron microenvironment due to their role in glucose metabolism, blood-brain barrier, neurotransmitter-uptake, and synaptic development and maturation\textsuperscript{169-171}. Both rodent models and human postmortem studies strongly support this hypothesis. For example, rats exposed to maternal separation have lower density of astrocytes in the medial prefrontal cortex\textsuperscript{172}, and chronic social defeat reduces astrocyte count in various brain regions (prefrontal/frontal cortex, hippocampus and amygdala), lowering the levels of GFAP protein, an astrocyte marker\textsuperscript{173-174}. Likewise, selective lesion of glial astrocytes by infusing L-\alpha aminoadipic acid into rodent prefrontal cortex induces depressive-like behaviors\textsuperscript{175-176}.

Recently, the role of gut microbiota in affective disorders has been recognized\textsuperscript{177} to modulate multiple neural, endocrine and immune mechanisms\textsuperscript{178}, as shown using germ-free animals, bacterial infections or probiotics\textsuperscript{177}. Indeed, germ-free rodents display increased anxiety-\textsuperscript{179-180} and depression-like behaviors\textsuperscript{181}, as well as elevated noradrenaline, dopamine and serotonin turnover in the striatum\textsuperscript{182}. In contrast, treating germ-free animals with probiotics lowers their
anxiety and depression-like behaviors\textsuperscript{183-185}, currently considered as psychobiotics - live organisms that, when ingested in adequate amounts, produce a health benefit in patients suffering from psychiatric illness\textsuperscript{186}. Complementing gut microbiome involvement, depression is also linked to metabolic disorders, especially obesity and diabetes\textsuperscript{187-192}. While the exact mechanisms underlying this link remain unclear, some of the linked conditions, such as type 2 diabetes, may involve shared pathogenetic mechanisms including chronic activation of immune and neuroendocrine pathways\textsuperscript{192}. Animal studies are consistent with clinical data, since the Spontaneously Diabetic Torii (SDT) fatty rat model for type 2 diabetes shows increased depressive-like behavior, hyperlocomotion, higher basal corticosterone levels, lower serotonin and glutamate in prefrontal cortex, and higher GABA and glutamate levels in the hippocampus\textsuperscript{193}. Similar depression-like behavior can be observed in diabetes induced by streptozotocin in rats and reversed by antidepressant treatment\textsuperscript{194}. Some zebrafish models of diabetes and metabolic conditions also evoke anxiety-like behavior\textsuperscript{195-196}.

4. Conclusion

Depression-like behavioral phenotypes vary widely between strains and species, and therefore cross-strain/species translations of data should be performed carefully\textsuperscript{197}. Furthermore, individual differences in animal models also exist, and must be considered\textsuperscript{198}. In fact, rodents exhibit a wide population variety in depression-like behaviors, and can be selectively bred for depression-like traits (e.g., Flinders Sensitive Line, Swim Low-Active and Helpless Rouen strains)\textsuperscript{26, 199-213}. Another important point to consider is environmental characteristics, since environmental enrichment and impoverishment can influence individual affective phenotypes\textsuperscript{214}, and similar environmental modulation exists in animal depression models\textsuperscript{215-218}. As individual differences exist in evolutionarily distant species, such as rodents and zebrafish\textsuperscript{219-223}, individual behavioral, genetic and environmental factors must be monitored, to ensure correct interpretation of findings.

Recently, special attention has been given to drugs with putative rapid-acting antidepressant effects, affecting even patients resistant to conventional antidepressant treatments.
For example, the NMDA receptor antagonist ketamine\textsuperscript{224} within days reduces depressive symptoms\textsuperscript{225-228} and suicidal thoughts\textsuperscript{229} in patients, and exerts similar antidepressant effects in rodent FST, TST, inflammation-, stress- and learned helplessness-related models\textsuperscript{230-253}.

Ideally, modeling depression or other mental disorders would need to recreate the etiologic process in animals, thus replicating not only specific individual phenotypes of interest, but a wider spectrum of neural and behavioral features of the disorder in question\textsuperscript{254}. Given the fact that a model by itself is not a perfect replication of the condition studied, not all criteria can be met in a single model. Thus, combination of different models can more accurately address the condition of interest. Such cross-species paradigm can help understand the most common (and therefore core) features of diseases, as well as properly characterize distinct profiles observed in different species. Multispecies models of psychiatric diseases can introduce us to a principally new view of diseases in which neurobiological constructs play a leading role in pathogenesis. However, such models are yet to emerge and will rely on larger and more extensive cross-species studies.

5. Expert Opinion

Endophenotype-driven approaches as a locomotive for innovations in the field

While the lack of understating of pathogenesis of depression and other psychiatric disorders slows down further progress in the field, novel approaches continuously emerge\textsuperscript{255}. For example, a radical rethinking of current taxonomies is required for deeper understanding of psychiatric disorders\textsuperscript{256-258}. Endophenotype strategy reduces complex psychiatric conditions into directly measurable neurophysiological, neuropsychological, biochemical, endocrine, neuroanatomical or cognitive components\textsuperscript{259-261}. However, this approach is not sufficient to overcome limitations that emerge in the field, necessitating further strategies to bridge its translational and cross-disciplinary gaps\textsuperscript{262-264}. For example, the “cross-species trait genetic” approach postulates that simple behavioral endophenotypes should be conserved between species, including humans\textsuperscript{264}. However, the ‘spectrum’ nature of CNS disorders and their overlapping endophenotypes, behavioral symptoms and biomarkers should also be considered\textsuperscript{262-263}. Addressing this need, the “domain interplay” concept was suggested to further optimize animal
modeling of CNS disorders\textsuperscript{262}. Rather than simply focusing on specific behaviors or genes, this concept emphasizes the importance of analyzing several overlapping behavioral endophenotypes and interplay/dynamics between them\textsuperscript{262}.

For a rigorous and thorough animal modeling of depression, new approaches also necessitate higher-throughput protocols and test batteries\textsuperscript{265-267}. While common strategies utilize various specific tests to access key behavioral features of depression, another ‘smart’ approach may involve ‘hybrid’ behavioral models to speed up behavioral characterization\textsuperscript{268}. Such hybridizing approach assesses several different domains in the same test, or combines several single-domain tests in the way that maximizes the spectrum of simultaneously or collectively observed phenotypes per trial\textsuperscript{268}. For example, FST may be performed as part of the Morris Water maze, a well-established hippocampal memory test, thereby enabling a simultaneous assessment of both despair and cognitive responses related to depression\textsuperscript{268}. Likewise, further hybridization can be achieved by examining post-swimming self-grooming and locomotor behavior in a subsequently run open field (novelty-based) or small observation box, to detect phenotype associated with depression-like behavioral perseverations\textsuperscript{269} and/or examining per-minute behavioral activity in these tests, to study habituation (a working memory-related phenotypes) reflecting cognitive alterations in depression\textsuperscript{268, 270}.

Another important aspect to consider is the overall trajectory of the disorder. Indeed, neuropsychiatric phenomena are not instant, and cannot be treated separately from their development and dynamics \textsuperscript{271-272}. Albeit markedly understudied, dynamic models in biological psychiatry have recently received increasing attention. For example, the ‘interlinking genes’ approach can be used to address this problem\textsuperscript{262-263} since various disordered endophenotypes interact with each other, and may share common molecular ‘crosstalk’ mechanisms that, although not influencing the phenotypes by themselves, can confer their interrelatedness\textsuperscript{262-263}. Example of dynamic interactions in this case can be depression-like phenotypes developing during chronic stress after an initial anxiety-like pathological state has occurred. Specifically, the chronic social defeat model uses conspecific agonistic interactions between mice (most commonly, C57BL/6J)
to produce a lasting experience of defeat in chronically losing mice\textsuperscript{273-275}. The model is known to induce both anxiety-like and depression-like phenotypes\textsuperscript{276}. At the same time, while increased anxiety can be observed at 3-10 days of chronic stress\textsuperscript{277}, depression-like phenotype is usually induced after 20-21 days of such antagonistic interactions\textsuperscript{278}. Therefore, development of anxiety precedes the development of depression in the chronic social stress model; interestingly, this is often true for depressed patients, as anxiety can trigger depression in 15-33\% of patients\textsuperscript{278}. Thus, anxiety states can lead to depression states both clinically and in animal models, and molecular and physiological pathways that provide transition between these phenotypes may be promising, yet to be identified, drug targets for future therapeutic interventions.

Another major problem that must be resolved is the apparent lack of coherent long-term goals of animal and human disease modeling and CNS drug discovery. For example, the ultimate goal of animal tests is to find the most effective therapeutic treatment, without major focus on its side effects. In contrast, human tests focus on drug safety much more then on drug efficacy. Like cats misread dog behaviors, such conceptual differences in models’ goals produce a well-documented low yield of CNS drug discovery\textsuperscript{279}, which not only stifles innovation in this field\textsuperscript{280}, but also begins to impact the field in the long-run, as many pharmaceutical giants continue to shut down their CNS drug discovery programs, and refocus on other, non-psychiatric diseases\textsuperscript{281}. The solution to this problem would be a better synchronization of research goals at pre- and clinical stages, for example, by including a drug safety component into preclinical drug discovery testing and by focusing more on drug efficacy during pilot clinical studies, with subsequent additional trials aimed at reducing drug side effects by testing safer analogs, metabolites or other derivatives once the high efficacy of the prototypic drug was established in both pre- and clinical trials. Thus, instead of proclaiming a novel promising drug a clinical failure due to its side-effects, a wiser strategy would be to screen for its safer compounds first, before making a final determination. Thus, the field of antidepressant drug screening can be reinvigorated and innovated, rather than suffer a gradual decline and decay.
Finally, we want to emphasize that, despite some limitations and complications that animal modeling and drug screening in biological psychiatry are facing, the field should not be left behind by clinical research. Animal models represent a valuable tool to assess deeply and maximally the neurobiological and genetic determinants of disorders. Thus, further innovation of biological methodology can complement recent clinical findings, and may soon lead to new comprehensive biomedical theories of depression.

Acknowledgments

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Figure 1. Bar chart representing frequency of common comorbid conditions with major depression\textsuperscript{14}.
Figure 2. Use of animal models of depression for 2003-2018, Pubmed searches [species] models of depression. In case of fishes, zebrafish, Carassius auratus, goldfish, Poecilia, Oryzias, Acipenser, salmon were used. In case of non-human primates, bonobos, chimpanzee and macaques were used. (A) Cumulative number of articles per year – can be clearly seen superiority of rodents’ models in translational depression research. (B) – Relative number of articles per year – was calculated as year n to year 2003 ratio in given category and expressed as percent. Can be seen faster relative growth of fish models that are novel for depression research.
Table 1. Example of major depression neuropathological subtypes that can be identified. Levels of severity were given depending on most frequent HAMD unit, where 0 — is minimal, for anergia, fatigue, insomnias — 2 is maximum, and for anxiety, anhedonia and psychomotor retardation 4 is maximum.

<table>
<thead>
<tr>
<th>Symptom Severity</th>
<th>Biotype 1</th>
<th>Biotype 2</th>
<th>Biotype 3</th>
<th>Biotype 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhedonia</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Moderate</td>
<td>Mild</td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Early Insomnia</td>
<td>Severe</td>
<td>Mild</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Middle Insomnia</td>
<td>Severe</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Anergia, Fatigue</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Table 2. Selected examples of rodents’ experimental models of major depression addressing distinct aspects of affective pathogenesis.

<table>
<thead>
<tr>
<th>Models types</th>
<th>Examples and aspect of pathogenesis targeted</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress-related</td>
<td>Early-life stress</td>
<td>24, 199, 282-285</td>
</tr>
<tr>
<td></td>
<td>Social stress</td>
<td>39-40, 60, 62, 81, 88, 150</td>
</tr>
<tr>
<td></td>
<td>Aggression</td>
<td>59, 88</td>
</tr>
<tr>
<td></td>
<td>Chronic stress</td>
<td>35-40</td>
</tr>
<tr>
<td>Genetic</td>
<td>Knockouts of the monoaminergic system genes</td>
<td>41-46</td>
</tr>
<tr>
<td></td>
<td>Knockouts of the HPA-related genes</td>
<td>47-49</td>
</tr>
<tr>
<td></td>
<td>Selectively bred for helplessness or despair</td>
<td>202-203, 206-208</td>
</tr>
<tr>
<td>Inflammation-related</td>
<td>Genetic ablation of inflammation-related genes</td>
<td>50-53</td>
</tr>
<tr>
<td></td>
<td>Exposure to inflammatory agents, ‘sickness behavior’</td>
<td>83-86, 91-93</td>
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<tr>
<td></td>
<td>Gut microbiota models</td>
<td>180-181, 286</td>
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<tr>
<td>Monoamine depletion</td>
<td>Dopaminergic toxins</td>
<td>37, 77, 81, 137</td>
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<tr>
<td></td>
<td>Reserpine-induce</td>
<td>287-288</td>
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<tr>
<td>Drug abuse-related</td>
<td>Chronic treatment with substances of abuse</td>
<td>127, 224</td>
</tr>
<tr>
<td></td>
<td>Drug withdrawal</td>
<td>54-56</td>
</tr>
</tbody>
</table>

HPA - hypothalamic-pituitary-adrenal axis
Table 3. Selected non-rodent models for studying neurobiological conditions

<table>
<thead>
<tr>
<th>Model</th>
<th>Non-human primates</th>
<th>Fish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress-induced</td>
<td>Chronic stress induced affective disruptions\textsuperscript{140}, especially effective are social stress models, such as separation\textsuperscript{122-127}</td>
<td>Acute\textsuperscript{289} or chronic stress\textsuperscript{148-149, 151, 290} exposure, including social stress\textsuperscript{291}, may lead to affective deficits and disrupted HPA axis\textsuperscript{148-149, 151, 289-290} (sensitive to antidepressant treatments\textsuperscript{151})</td>
</tr>
<tr>
<td>Pharmacological</td>
<td>G-methyl-p-tyrosine or reserpine may reduce social interactions and locomotion, as well as induce anhedonia-like lack of environmental interaction\textsuperscript{126, 131}</td>
<td>Repeated intake of psychostimulants provokes behavioral sensitization\textsuperscript{292}. Chronic exposure to reserpine\textsuperscript{293}, rotenone\textsuperscript{294} or SiO\textsubscript{2} nanoparticles\textsuperscript{295} evokes depression-like behaviors</td>
</tr>
<tr>
<td>Genetic</td>
<td>Interactions between the serotonin transporter gene-linked polymorphic region (5-HTTLPR) polymorphisms and rearing type have been linked to different behaviors associated with stress\textsuperscript{121}</td>
<td>Knockout of the GR gene causes elevation of whole-body cortisol levels and changes exploration and habituation behavior\textsuperscript{296-297}</td>
</tr>
</tbody>
</table>

HPA - hypothalamic-pituitary-adrenal axis
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