

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 disability¹. Depression is a highly heterogeneous clinical disorder the diagnosis of which is complicated due to broad phenomenological criteria and poorly understood neurobiological bases²⁻⁵. Associated with mood-, appetite-, sleep-, energy-, cognitive-, motor- and other deficits, depression symptoms may be grouped into several distinct neuropathological subtypes²(Table 1). Thus, clinical or preclinical modeling of depression is complicated by the fact that we deal with multiple ‘depressions’⁶⁻⁸.

Another problem is that approximately 1/3 of depressed patients are treatment-resistant, and the disorder has high rates of recurrence⁹⁻¹³ and comorbidity with other brain illnesses¹⁴⁻¹⁵ (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, 16}. However, this becomes a particularly challenging task, given the lack of pathophysiological understanding of this disease. Indeed, the most widely accepted monoamine imbalance hypotheses¹⁷⁻¹⁸ cannot account for limitations discussed above (delayed effects, treatment resistance), and recently proposed ‘inflammation’ hypotheses¹⁹⁻²¹ 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, 22-23}.

Animal (experimental) models are an indispensable tool in translational and neuroscience research²³⁻²⁴, relying on several well-recognized validity criteria, such as face (similarity of phenotypes), construct (similarity of neurobiological mechanisms) and predictive (similarity of treatment responsiveness) validity^{10, 25-27}. For clear ethical, practical and historical reasons, most research utilizes rodents to study depression and other affective disorders^{10, 28-34} (Fig. 2). Rodent models of depression are relatively well-established, and target different aspects of depression (Table 2), including stress³⁵⁻⁴⁰, genetics⁴¹⁻⁴⁹, inflammation⁵⁰⁻⁵³ and drug responses⁵⁴⁻⁵⁶. 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-1 β , IL-6, TNF- α) and decrease neurotrophins (e.g., BDNF and NGF) in the brain – the effects which can be reversed by antidepressant treatment^{23, 35-40, 57-64}. Since stress is the most common factor of depression onset and progression^{26, 57}, high face and construct validity, predictive power and relative simplicity make stress-based models widely used to model depression^{23, 65}.

While genetic vulnerability plays a role in 35–40% of variance in depression⁶⁶, human genetic analyses often fail to identify reproducible genetic loci that contribute significantly to depression⁶⁷. 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 pathways⁶⁸. Genetic rodent models indicate the role of serotonergic⁴¹⁻⁴⁴, noradrenergic^{45-46, 69-70}, dopaminergic⁷¹⁻⁷², opioid⁷³⁻⁷⁴, GABA-ergic^{10, 75-76} and glutamatergic⁷⁷⁻⁸⁰ 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 x environment interactions (GxE), acting as a susceptibility and a trigger, respectively⁸¹⁻⁸².

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 retardation³¹. This effect involves cytokine signaling pathways³¹ and can be induced by a wide range of agents, including polysaccharide (LPS)⁸³⁻⁸⁹, viral mimetic polyriboinosinic-polyribocytidylic acid (Poly I:C)⁹⁰, interferon (IFN)- α ⁹¹⁻⁹³ and bacillus Calmette-Guerin (BCG)⁹⁴⁻⁹⁵. Some overlaps between drug withdrawal and depression also exist⁹⁶ and have been reported in rodents for cocaine, amphetamine, ethanol, morphine and nicotine⁵⁴⁻⁵⁶ (also note hypomania following antidepressant discontinuation both in clinical practice and animal models⁹⁷⁻⁹⁸).

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^{10, 24, 99-116}. 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)^{114, 116-117} and the tail suspension test (TST)^{112, 118} are commonly used to assess 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 models¹¹⁹. 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 drug 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 models¹²⁰⁻¹²¹, 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 maternal¹²²⁻¹²³ or social separation¹²⁴⁻¹²⁵ and reflect various aspects of human

depression¹²⁶, such as despair, anhedonia and lethargy¹²⁷. Such models are validated pharmacologically, and, interestingly, antidepressants seem to have similar time course to that observed clinically (unlike in some rodent models)¹²⁸⁻¹²⁹. Other drugs, including amphetamine and ethanol, exert antidepressant effects in non-human primates^{127, 130}, whereas *α*-methyl-*p*-tyrosine or reserpine reduce social interactions and locomotion, as well as induce anhedonia-like lack of environmental interaction^{126, 131}. Interestingly, depressive behaviors can occur in macaques spontaneously¹³², strikingly reproducing human depression. Likewise, neurochemical alterations in primate oxytocin, monoamines and their metabolites also resemble alterations observed in depressed patients¹³³⁻¹³⁹. Finally, non-human primates are also used to model depressive behavior in chronic stress¹⁴⁰ and cytokine-induced depression¹⁴¹.

Among lower vertebrates, zebrafish represent an interesting model organism to study complex CNS states¹⁴²⁻¹⁴⁶, including anxiety, addiction, autism, obsessive-compulsive states and depression¹⁴²⁻¹⁴⁶. Similarly to rodents, zebrafish depression-like states can be induced using stress, genetic or pharmacological manipulations¹⁴⁷ (Table 3). For instance, zebrafish chronic stress exposure elevates anxiety-related behavior, increases whole-body cortisol, IL-1 β , IL-6, adenosine, *m*, *gr* α , *gr* β , *bdnf* in telencephalon, CRH, calcineurine, pCREB levels in brain, alters dendritic spines, reduces weight, and lowers dopamine and 5-HIAA levels¹⁴⁸⁻¹⁵³. Importantly, many of these effects can be corrected by antidepressant treatment¹⁵¹, 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 models¹⁵¹), 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 rodents¹⁵⁴, 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)¹⁴⁷, 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 monoamine¹⁵⁵⁻¹⁵⁶, and 1969, when it was first linked to depression¹⁵⁵, 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_{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^{113, 157-158}, whereas 5-HT_{1A} knockout in mice display antidepressant-like behavior^{29, 159-160} and serotonin transporter knockout rodents display anxiety-like and higher stress vulnerability⁴¹⁻⁴⁴.

Another hypothesis of depression is based upon inflammation caused by stress, as the expression of IL-1 β , IL-6, TNF- α and IFN- γ genes were significantly higher in patients with major depression¹⁶¹⁻¹⁶². Furthermore, elevated stress hormones can impact the expression of several neurotrophic factors, thus influencing on neuroplasticity, which is impaired in depressed patients¹⁶¹. Likewise, the hypothalamic–pituitary–adrenal (HPA) axis function is altered in depressed patients as well as in depressed rodent models, and reversed by antidepressant treatment¹⁶¹. Likewise, disturbances of affective spectrum can occur after exposure to inflammatory agents (e.g., lipopolysaccharide (LPS)⁸³⁻⁸⁶, viral mimetic polyriboinosinic-polyribocytidylic acid⁹⁰ and some autoantibodies¹⁶³) or as a result of genetic manipulations of pro/anti-inflammation-related genes (e.g., *IL-10*⁵¹⁻⁵³ and *TNF- α* knockout models⁵⁰). In line with this, anti-inflammatory agents can reduce depressive symptoms in humans¹⁶⁴ 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 mice¹⁶⁵. 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^{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 gene¹⁶¹. Consistent with this, major depression is generally accompanied by reduced GABA levels, which can be restored by conventional antidepressant treatments¹⁶¹. 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^{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 depression¹⁶⁶⁻¹⁶⁸. Indeed, astrocytes are crucial to neuron microenvironment due to their role in glucose metabolism, blood-brain barrier, neurotransmitter-uptake, and synaptic development and maturation¹⁶⁹⁻¹⁷¹. 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 cortex¹⁷², 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 marker¹⁷³⁻¹⁷⁴. Likewise, selective lesion of glial astrocytes by infusing L- α amino adipic acid into rodent prefrontal cortex induces depressive-like behaviors¹⁷⁵⁻¹⁷⁶.

Recently, the role of gut microbiota in affective disorders has been recognized¹⁷⁷ to modulate multiple neural, endocrine and immune mechanisms¹⁷⁸, as shown using germ-free animals, bacterial infections or probiotics¹⁷⁷. Indeed, germ-free rodents display increased anxiety-¹⁷⁹⁻¹⁸⁰ and depression-like behaviors¹⁸¹, as well as elevated noradrenaline, dopamine and serotonin turnover in the striatum¹⁸². In contrast, treating germ-free animals with probiotics lowers their

anxiety and depression-like behaviors¹⁸³⁻¹⁸⁵, currently considered as psychobiotics - live organisms that, when ingested in adequate amounts, produce a health benefit in patients suffering from psychiatric illness¹⁸⁶. Complementing gut microbiome involvement, depression is also linked to metabolic disorders, especially obesity and diabetes¹⁸⁷⁻¹⁹². 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 pathways¹⁹². 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 hippocampus¹⁹³. Similar depression-like behavior can be observed in diabetes induced by streptozotocin in rats and reversed by antidepressant treatment¹⁹⁴. Some zebrafish models of diabetes and metabolic conditions also evoke anxiety-like behavior¹⁹⁵⁻¹⁹⁶.

4. Conclusion

Depression-like behavioral phenotypes vary widely between strains and species, and therefore cross-strain/species translations of data should be performed carefully¹⁹⁷. Furthermore, individual differences in animal models also exist, and must be considered¹⁹⁸. 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)¹⁹⁹⁻²¹³. Another important point to consider is environmental characteristics, since environmental enrichment and impoverishment can influence individual affective phenotypes²¹⁴, and similar environmental modulation exists in animal depression models²¹⁵⁻²¹⁸. As individual differences exist in evolutionarily distant species, such as rodents and zebrafish²¹⁹⁻²²³, 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 ketamine²²⁴ within days reduces depressive symptoms²²⁵⁻²²⁸ and suicidal thoughts²²⁹ in patients, and exerts similar antidepressant effects in rodent FST, TST, inflammation-, stress- and learned helplessness-related models²³⁰⁻²⁵³.

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 question²⁵⁴. 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 emerge²⁵⁵. For example, a radical rethinking of current taxonomies is required for deeper understanding of psychiatric disorders²⁵⁶⁻²⁵⁸. Endophenotype strategy reduces complex psychiatric conditions into directly measurable neurophysiological, neuropsychological, biochemical, endocrine, neuroanatomical or cognitive components²⁵⁹⁻²⁶¹. However, this approach is not sufficient to overcome limitations that emerge in the field, necessitating further strategies to bridge its translational and cross-disciplinary gaps²⁶²⁻²⁶⁴. For example, the “cross-species trait genetic” approach postulates that simple behavioral endophenotypes should be conserved between species, including humans²⁶⁴. However, the ‘spectrum’ nature of CNS disorders and their overlapping endophenotypes, behavioral symptoms and biomarkers should also be considered²⁶²⁻²⁶³. Addressing this need, the “domain interplay” concept was suggested to further optimize animal

modeling of CNS disorders²⁶². Rather than simply focusing on specific behaviors or genes, this concept emphasizes the importance of analyzing several overlapping behavioral endophenotypes and interplay/dynamics between them²⁶².

For a rigorous and thorough animal modeling of depression, new approaches also necessitate higher-throughput protocols and test batteries²⁶⁵⁻²⁶⁷. 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 characterization²⁶⁸. 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 trial²⁶⁸. 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 depression²⁶⁸. 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 perseverations²⁶⁹ and/or examining per-minute behavioral activity in these tests, to study habituation (a working memory-related phenotypes) reflecting cognitive alterations in depression^{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 dynamics²⁷¹⁻²⁷². 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 problem²⁶²⁻²⁶³ 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 interrelatedness²⁶²⁻²⁶³. 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 mice²⁷³⁻²⁷⁵. The model is known to induce both anxiety-like and depression-like phenotypes²⁷⁶. At the same time, while increased anxiety can be observed at 3-10 days of chronic stress²⁷⁷, depression-like phenotype is usually induced after 20-21 days of such antagonistic interactions²⁷⁸. 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 patients²⁷⁸. 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 than on drug efficacy. Like cats misread dog behaviors, such conceptual differences in models' goals produce a well-documented low yield of CNS drug discovery²⁷⁹, which not only stifles innovation in this field²⁸⁰, 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 diseases²⁸¹. 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.

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Figure 1. Bar chart representing frequency of common comorbid conditions with major depression¹⁴.

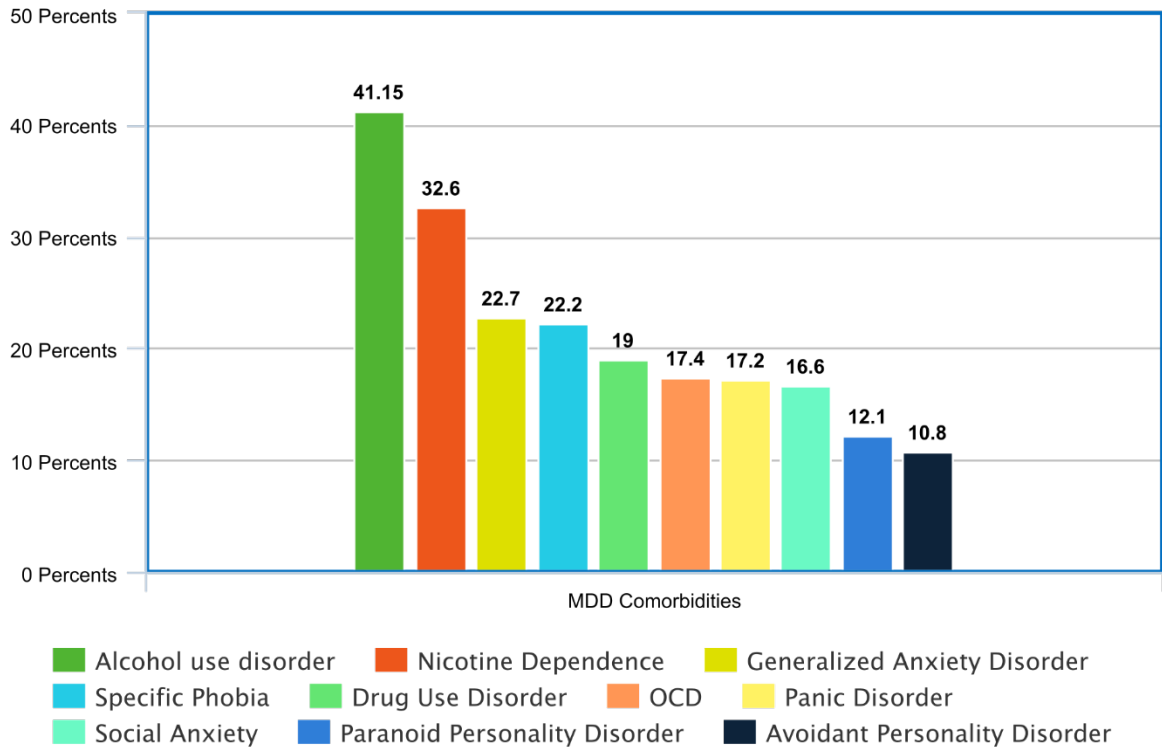
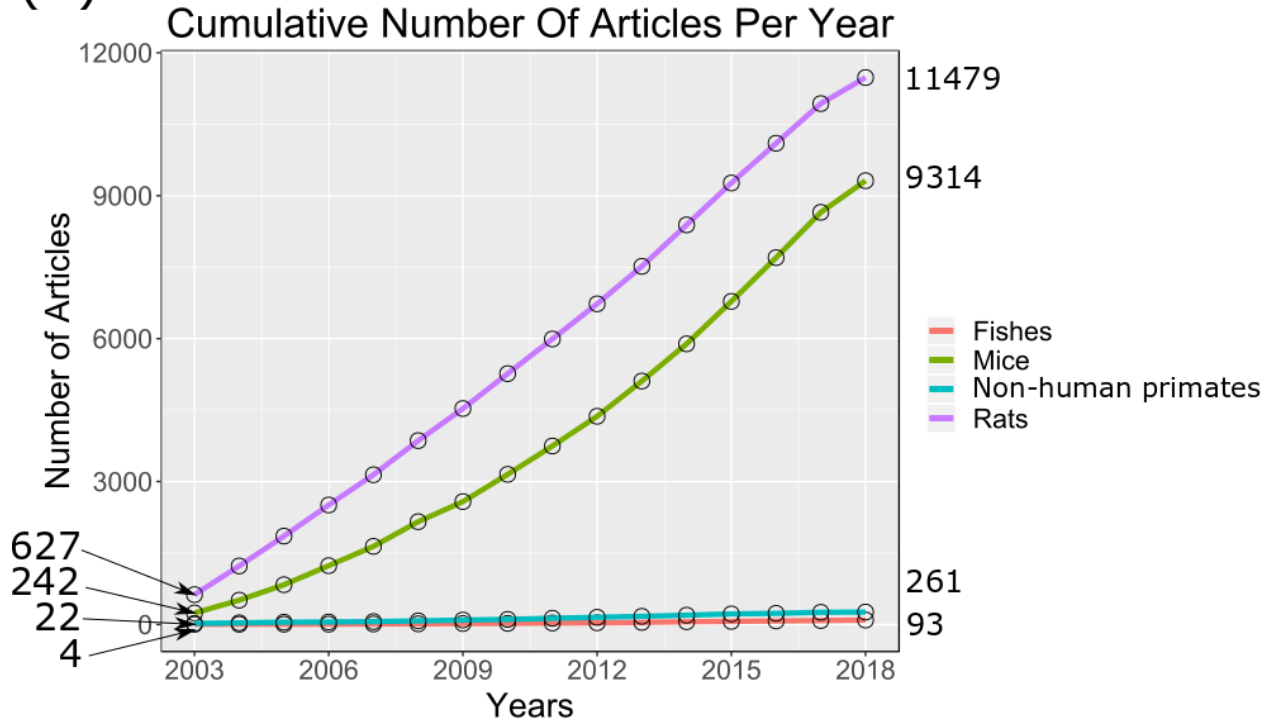


Figure 2. Use of animal models of depression for 2003-2018, Pubmed searches [species] models of depression. In case of fishes, zebrafish, *Carassius auratus*, goldfish, *Poecilia*, *Oryzias*, *Acipenser*, salmon were used. In case of non-human primates, bonobos, chimpanzee and macaques were used. (A) 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.

(A)



(B)

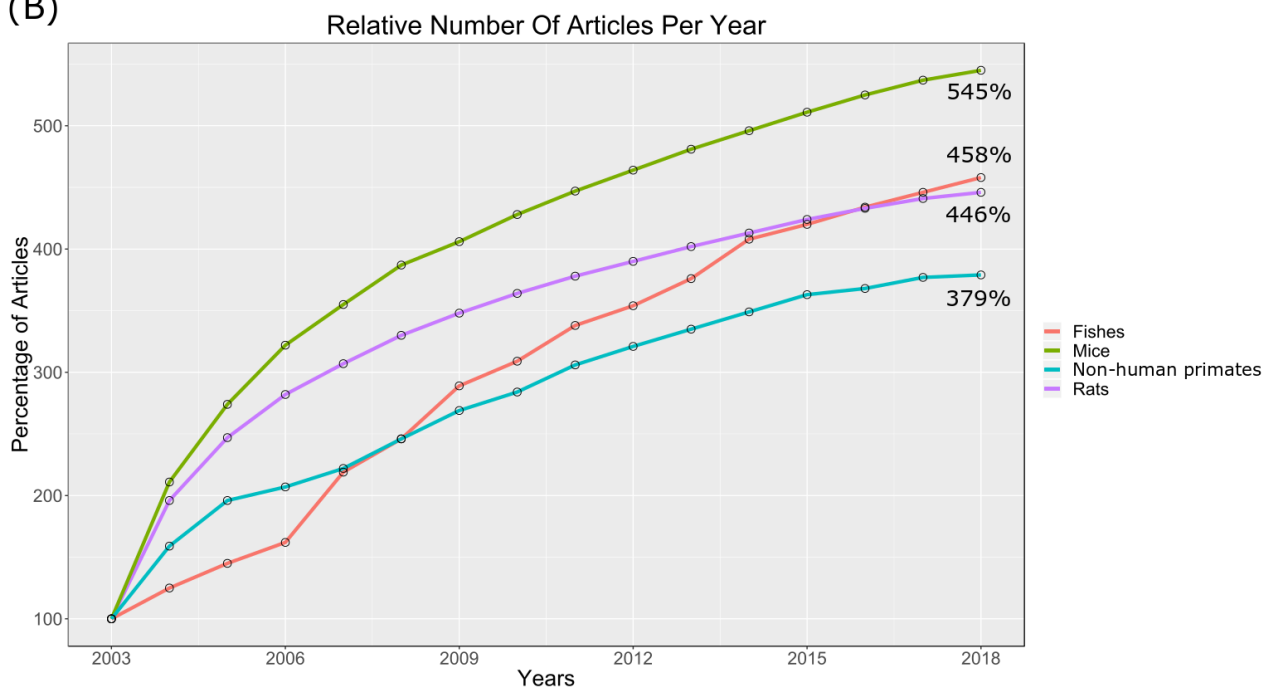


Table 1. Example of major depression neuropathological subtypes that can be identified². Levels of severity were given depending on most frequent HAMD unit, where 0 — is minimal, for anergia, fatigue, insomnias — 2 is maximum, and for anxiety, anhedonia and psychomotor retardation 4 is maximum².

Symptom Severity	Biotype 1	Biotype 2	Biotype 3	Biotype 4
Anhedonia	Moderate	Moderate	Severe	Severe
Psychomotor retardation	Mild	Mild	Mild	Mild
Anxiety	Moderate	Mild	Mild	Moderate
Early Insomnia	Severe	Mild	Severe	Severe
Middle Insomnia	Severe	Mild	Moderate	Severe
Anergia, Fatigue	Severe	Severe	Moderate	Moderate

Table 2. Selected examples of rodents’ experimental models of major depression addressing distinct aspects of affective pathogenesis.

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

HPA - hypothalamic-pituitary-adrenal axis

Table 3. Selected non-rodent models for studying neurobiological conditions

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

HPA - hypothalamic-pituitary-adrenal axis

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