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[2-5]. 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'[6-8].

Another problem is that approximately 1/3 of depressed patients are treatment-resistant, and the disorder has high rates of recurrence[9-13] and comorbidity with other brain illnesses[14-15] (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 hypotheses[17-18] cannot account for limitations discussed above (delayed effects, treatment resistance), and recently proposed 'inflammation' hypotheses[19-21] 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 research[23-24], 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, 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 stress[35-40], genetics[41-49], inflammation[50-53] and drug responses[54-56]. 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[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 depression[66], human genetic analyses often fail to identify reproducible genetic loci that contribute significantly to depression[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[68]. Genetic rodent models indicate the role of serotonergic[41-44], noradrenergic[45-46, 69-70], dopaminergic[71-72], opioid[73-74], GABA-ergic[10, 75-76] and glutamatergic[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 x environment interactions (GxE), acting as a susceptibility and a trigger, respectively[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[31]. This effect involves cytokine signaling pathways[31] 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 exist[96] and have been reported in rodents for cocaine, amphetamine, ethanol, morphine and nicotine[54-56] (also note hypomania following antidepressant discontinuation both in clinical practice and animal models[97-98]).

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 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[119]. 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[120-121], 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 maternal[122-123] or social separation [124-125] and reflect various aspects of human

depression[126], such as despair, anhedonia and lethargy[127]. 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 g-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 spontaneously[132], strikingly reproducing human depression. Likewise, neurochemical alterations in primate oxytocin, monoamines and their metabolites also resemble alterations observed in depressed patients[133-139]. Finally, non-human primates are also used to model depressive behavior in chronic stress[140] and cytokine-induced depression[141].

Among lower vertebrates, zebrafish represent an interesting model organism to study complex CNS states[142-146], including anxiety, addiction, autism, obsessive-compulsive states and depression[142-146]. Similarly to rodents, zebrafish depression-like states can be induced using stress, genetic or pharmacological manipulations[147] (Table 3). For instance, zebrafish chronic stress exposure elevates anxiety-related behavior, increases whole-body cortisol, IL-1β, IL-6, adenosine, mr, grα, grβ, bdnf in telencephalon, CRH, calcineurine, pCREB levels in brain, alters dendritic spines, reduces weight, and lowers dopamine and 5-HIAA levels[148-153]. Importantly, many of these effects can be corrected by antidepressant treatment[151], 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[151]), 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[154], 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 monoamine[155-156], and 1969, when it was first linked to depression[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_{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 vulnerability[41-44].

Another hypothesis of depression is based upon inflammation caused by stress, as the expression of IL-1β, IL-6, TNF-α and IFN-ɣ genes were significantly higher in patients with major depression[161-162]. Furthermore, elevated stress hormones can impact the expression of several neurotrophic factors, thus influencing on neuroplasticity, which is impaired in depressed patients[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[161]. Likewise, disturbances of affective spectrum can occur after exposure to inflammatory agents (e.g., lipopolysaccharide (LPS)[83-86], viral mimetic polyriboinosinic-polyribocytidylic acid[90] and some autoantibodies[163]) or as a result of genetic manipulations of pro/anti-inflammation-related genes (e.g., *IL-10*[51-53] and *TNF-α* knockout models[50]). In line with this, anti-inflammatory agents can reduce depressive symptoms in humans[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[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[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[161]. Consistent with this, major depression is generally accompanied by reduced GABA levels, which can be restored by conventional antidepressant treatments[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[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[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[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[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[173-174]. Likewise, selective lesion of glial astrocytes by infusing L-α aminoadipic acid into rodent prefrontal cortex induces depressive-like behaviors[175-176].

Recently, the role of gut microbiota in affective disorders has been recognized[177] to modulate multiple neural, endocrine and immune mechanisms[178], as shown using germ-free animals, bacterial infections or probiotics[177]. Indeed, germ-free rodents display increased anxiety-[179-180] and depression-like behaviors[181], as well as elevated noradrenaline, dopamine and serotonin turnover in the striatum[182]. In contrast, treating germ-free animals with probiotics lowers their

anxiety and depression-like behaviors[183-185], currently considered as psychobiotics - live organisms that, when ingested in adequate amounts, produce a health benefit in patients suffering from psychiatric illness[186]. Complementing gut microbiome involvement, depression is also linked to metabolic disorders, especially obesity and diabetes[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 parhways[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[193]. Similar depression-like behavior can be observed in diabetes induced by streptozotocin in rats and reversed by antidepressant treatment[194]. Some zebrafish models of diabetes and metabolic conditions also evoke anxiety-like behavior[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[197]. Furthermore, individual differences in animal models also exist, and must be considered[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) [26, 199-213]. Another important point to consider is environmental characteristics, since environmental enrichment and impoverishment can influence individual affective phenotypes[214], and similar environmental modulation exists in animal depression models[215-218]. As individual differences exist in evolutionarily distant species, such as rodents and zebrafish[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[224] within days reduces depressive symptoms[225-228] and suicidal thoughts[229] in patients, and exerts similar antidepressant effects in rodent FST, TST, inflammation-, stress- and learned helplessness-related models[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[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[255]. For example, a radical rethinking of current taxonomies is required for deeper understanding of psychiatric disorders[256-258]. Endophenotype strategy reduces complex psychiatric conditions into directly measurable neurophysiological, neuropsychological, biochemical, endocrine, neuroanatomical or cognitive components[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[262-264]. For example, the “cross-species trait genetic” approach postulates that simple behavioral endophenotypes should be conserved between species, including humans[264]. However, the ‘spectrum’ nature of CNS disorders and their overlapping endophenotypes, behavioral symptoms and biomarkers should also be considered[262-263]. Addressing this need, the “domain interplay” concept was suggested to further optimize animal

modeling of CNS disorders[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[262].

For a rigorous and thorough animal modeling of depression, new approaches also necessitate higher-throughput protocols and test batteries[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[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[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[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[269] 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 dynamics [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[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[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[273-275]. The model is known to induce both anxiety-like and depression-like phenotypes[276]. At the same time, while increased anxiety can be observed at 3-10 days of chronic stress[277], depression-like phenotype is usually induced after 20-21 days of such antagonistic interactions[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[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 [279], which not only stifles innovation in this field[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[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.

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Figure 1. Bar chart representing frequency of common comorbid conditions with major depression[14].

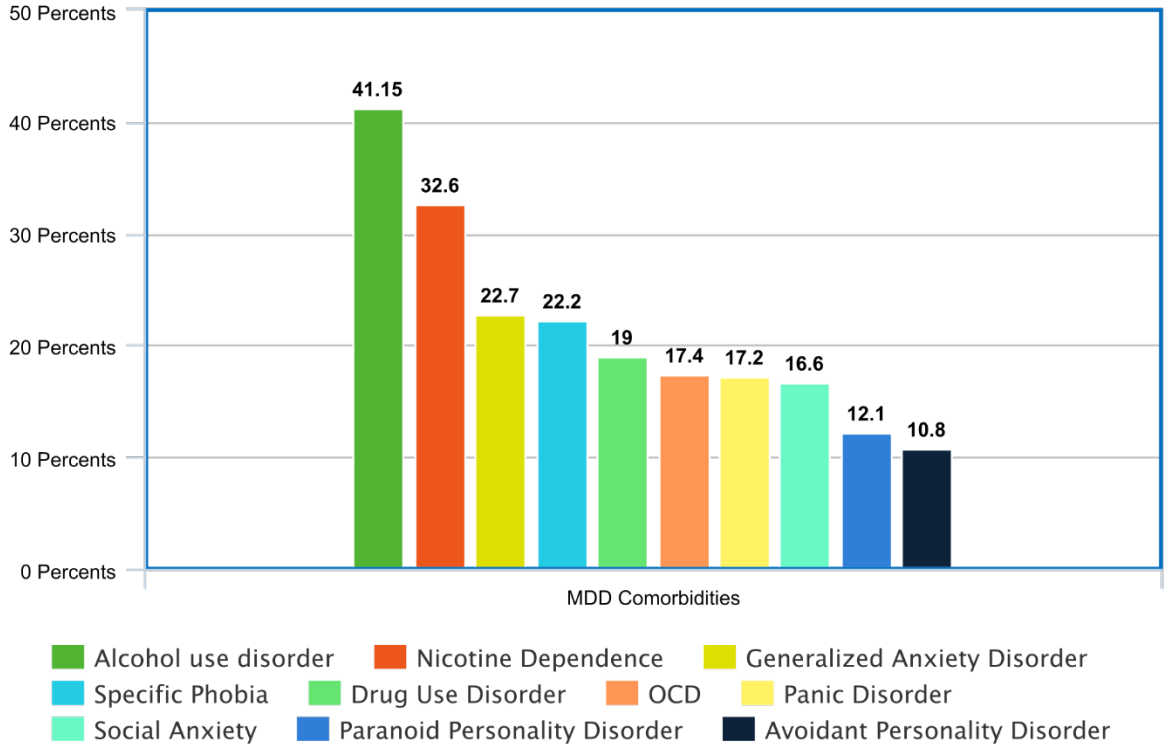

Figure 2. Use of animal models of depression for 2003-2018, Pubmed searches [species] models of depression. In case of fishes, zebrafish, Carassius auratus, goldfish, Poecilia, Oryzias, Acipenser, salmon were used. In case of non-human primates, bonobos, chimpanzee and macaques were used. (A) Cumulative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

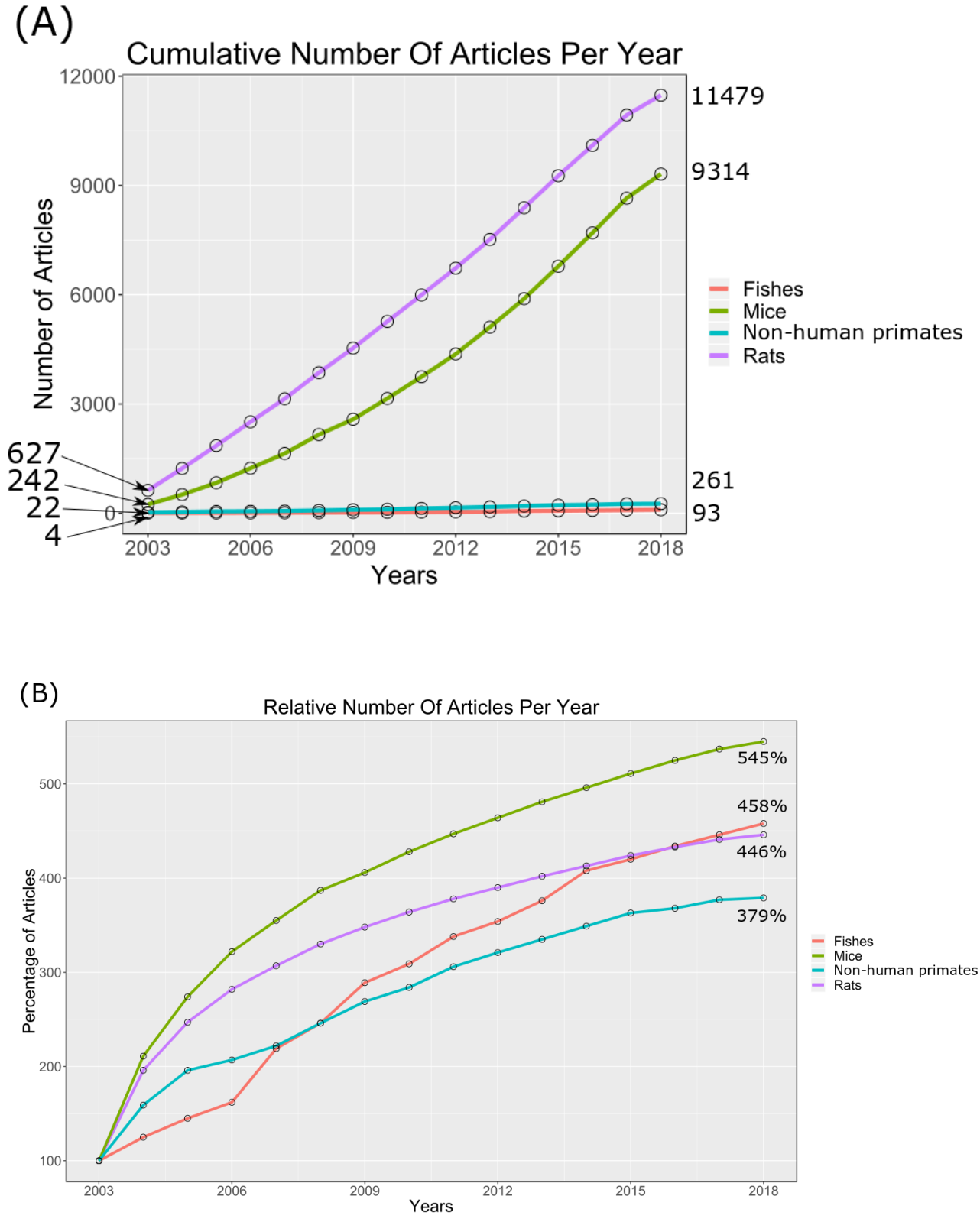

Table 1. Example of major depression neuropathological subtypes that can be identified[2]. Levels of severity were given depending on most frequent HAMD unit, where 0 — is minimal, for anergia, fatigue, insomnias — 2 is maximum, and for anxiety, anhedonia and psychomotor retardation 4 is maximum[2].

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

References

1. Organization, W. H., Depression and other common mental disorders: global health estimates. **2017**.
2. Drysdale, A. T.; Grosenick, L.; Downar, J.; Dunlop, K.; Mansouri, F.; Meng, Y.; Fetcho, R. N.; Zebley, B.; Oathes, D. J.; Etkin, A.; Schatzberg, A. F.; Sudheimer, K.; Keller, J.; Mayberg, H. S.; Gunning, F. M.; Alexopoulos, G. S.; Fox, M. D.; Pascual-Leone, A.; Voss, H. U.; Casey, B. J.; Dubin, M. J.; Liston, C., Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* **2017,** *23* (1), 28-38.
3. Insel, T. R.; Cuthbert, B. N., Medicine. Brain disorders? Precisely. *Science* **2015,** *348* (6234), 499-500.
4. Nestler, E. J.; Hyman, S. E., Animal models of neuropsychiatric disorders. *Nat Neurosci* **2010,** *13* (10), 1161-9.
5. Duman, R. S.; Aghajanian, G. K.; Sanacora, G.; Krystal, J. H., Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med* **2016,** *22* (3), 238-49.
6. Tokuda, T.; Yoshimoto, J.; Shimizu, Y.; Okada, G.; Takamura, M.; Okamoto, Y.; Yamawaki, S.; Doya, K., Identification of depression subtypes and relevant brain regions using a data-driven approach. *Scientific reports* **2018,** *8* (1), 14082.
7. de Vos, S.; Wardenaar, K. J.; Bos, E. H.; Wit, E. C.; de Jonge, P., Decomposing the heterogeneity of depression at the person-, symptom-, and time-level: latent variable models versus multimode principal component analysis. *BMC Medical Research Methodology* **2015,** *15* (1), 88.
8. van Loo, H. M.; de Jonge, P.; Romeijn, J.-W.; Kessler, R. C.; Schoevers, R. A., Data-driven subtypes of major depressive disorder: a systematic review. *BMC Medicine* **2012,** *10* (1), 156.
9. Rush, A. J.; Trivedi, M. H.; Wisniewski, S. R.; Nierenberg, A. A.; Stewart, J. W.; Warden, D.; Niederehe, G.; Thase, M. E.; Lavori, P. W.; Lebowitz, B. D.; McGrath, P. J.; Rosenbaum, J. F.; Sackeim, H. A.; Kupfer, D. J.; Luther, J.; Fava, M., Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* **2006,** *163* (11), 1905-17.
10. Cryan, J. F.; Mombereau, C., In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. *Mol Psychiatry* **2004,** *9* (4), 326-57.
11. Huynh, N. N.; McIntyre, R. S., What Are the Implications of the STAR*D Trial for Primary Care? A Review and Synthesis. *Prim Care Companion J Clin Psychiatry* **2008,** *10* (2), 91-6.
12. Insel, T. R.; Charney, D. S., Research on major depression: strategies and priorities. *JAMA* **2003,** *289* (23), 3167-8.
13. Wong, M. L.; Licinio, J., From monoamines to genomic targets: a paradigm shift for drug discovery in depression. *Nat Rev Drug Discov* **2004,** *3* (2), 136-51.
14. Blanco, C.; Okuda, M.; Markowitz, J. C.; Liu, S.-M.; Grant, B. F.; Hasin, D. S., The Epidemiology of Chronic Major Depressive Disorder and Dysthymic Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of clinical psychiatry* **2010,** *71* (12), 1645-1656.
15. Zahn–Waxler, C.; Klimes–Dougan, B.; Slattery, M. J., Internalizing problems of childhood and adolescence: Prospects, pitfalls, and progress in understanding the development of anxiety and depression. *Development and psychopathology* **2000,** *12* (3), 443-466.
16. Czeh, B.; Fuchs, E.; Wiborg, O.; Simon, M., Animal models of major depression and their clinical implications. *Prog Neuropsychopharmacol Biol Psychiatry* **2016,** *64*, 293-310.
17. Schildkraut, J. J., The catecholamine hypothesis of affective disorders: a review of supporting evidence. *American journal of Psychiatry* **1965,** *122* (5), 509-522.
18. Lapin, I.; Oxenkrug, G., Intensification of the central serotoninergic processes as a possible determinant of the thymoleptic effect. *The Lancet* **1969,** *293* (7586), 132-136.
19. Miller, A. H.; Raison, C. L., The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology* **2016,** *16* (1), 22.

20. Slavich, G. M.; Irwin, M. R., From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull* **2014,** *140* (3), 774-815.
21. Felger, J. C.; Lotrich, F. E., Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience* **2013,** *246*, 199-229.
22. Insel, T. R.; Voon, V.; Nye, J. S.; Brown, V. J.; Altevogt, B. M.; Bullmore, E. T.; Goodwin, G. M.; Howard, R. J.; Kupfer, D. J.; Malloch, G.; Marston, H. M.; Nutt, D. J.; Robbins, T. W.; Stahl, S. M.; Tricklebank, M. D.; Williams, J. H.; Sahakian, B. J., Innovative solutions to novel drug development in mental health. *Neurosci Biobehav Rev* **2013,** *37* (10 Pt 1), 2438-44.
23. Ma, L.; Demin, K. A.; Kolesnikova, T. O.; Kharsko, S. L.; Zhu, X.; Yuan, X.; Song, C.; Meshalkina, D. A.; Leonard, B. E.; Tian, L.; Kalueff, A. V., Animal inflammation-based models of depression and their application to drug discovery. *Expert Opin Drug Discov* **2017,** *12* (10), 995-1009.
24. Schmidt, M. V.; Wang, X. D.; Meijer, O. C., Early life stress paradigms in rodents: potential animal models of depression? *Psychopharmacology (Berl)* **2011,** *214* (1), 131-40.
25. Willner, P., *Behavioural models in psychopharmacology: theoretical, industrial and clinical perspectives*. Cambridge University Press: 1991.
26. Willner, P.; Mitchell, P. J., The validity of animal models of predisposition to depression. *Behav Pharmacol* **2002,** *13* (3), 169-88.
27. Anisman, H.; Matheson, K., Stress, depression, and anhedonia: caveats concerning animal models. *Neurosci Biobehav Rev* **2005,** *29* (4-5), 525-46.
28. Bechtholt, A. J.; Lucki, I., Effects of Serotonin-Related Gene Deletion on Measures of Anxiety, Depression, and Neurotransmission. In *The Serotonin Receptors: From Molecular Pharmacology to Human Therapeutics*, Roth, B. L., Ed. Humana Press: Totowa, NJ, 2006; pp 577-606.
29. Mohammad, F.; Ho, J.; Woo, J. H.; Lim, C. L.; Poon, D. J.; Lamba, B.; Claridge-Chang, A., Concordance and incongruence in preclinical anxiety models: Systematic review and meta-analyses. *Neurosci Biobehav Rev* **2016,** *68*, 504-29.
30. Kreiner, G.; Chmielarz, P.; Roman, A.; Nalepa, I., Gender differences in genetic mouse models evaluated for depressive-like and antidepressant behavior. *Pharmacol Rep* **2013,** *65* (6), 1580-90.
31. Dantzer, R.; O'Connor, J. C.; Freund, G. G.; Johnson, R. W.; Kelley, K. W., From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* **2008,** *9* (1), 46-56.
32. Kane, M. J.; Angoa-Perez, M.; Briggs, D. I.; Sykes, C. E.; Francescutti, D. M.; Rosenberg, D. R.; Kuhn, D. M., Mice genetically depleted of brain serotonin display social impairments, communication deficits and repetitive behaviors: possible relevance to autism. *PLoS One* **2012,** *7* (11), e48975.
33. Angoa-Perez, M.; Kane, M. J.; Briggs, D. I.; Sykes, C. E.; Shah, M. M.; Francescutti, D. M.; Rosenberg, D. R.; Thomas, D. M.; Kuhn, D. M., Genetic depletion of brain 5HT reveals a common molecular pathway mediating compulsivity and impulsivity. *J Neurochem* **2012,** *121* (6), 974-84.
34. Angoa-Perez, M.; Kane, M. J.; Briggs, D. I.; Herrera-Mundo, N.; Sykes, C. E.; Francescutti, D. M.; Kuhn, D. M., Mice genetically depleted of brain serotonin do not display a depression-like behavioral phenotype. *ACS Chemical Neuroscience* **2014,** *5* (10), 908-19.
35. Elizalde, N.; Gil-Bea, F. J.; Ramirez, M. J.; Aisa, B.; Lasheras, B.; Del Rio, J.; Tordera, R. M., Long-lasting behavioral effects and recognition memory deficit induced by chronic mild stress in mice: effect of antidepressant treatment. *Psychopharmacology (Berl)* **2008,** *199* (1), 1-14.
36. Bhutani, M. K.; Bishnoi, M.; Kulkarni, S. K., Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes. *Pharmacol Biochem Behav* **2009,** *92* (1), 39-43.
37. Shi, C. G.; Wang, L. M.; Wu, Y.; Wang, P.; Gan, Z. J.; Lin, K.; Jiang, L. X.; Xu, Z. Q.; Fan, M., Intranasal administration of nerve growth factor produces antidepressant-like effects in animals. *Neurochem Res* **2010,** *35* (9), 1302-14.

38. Filho, C. B.; Jesse, C. R.; Donato, F.; Giacomeli, R.; Del Fabbro, L.; da Silva Antunes, M.; de Gomes, M. G.; Goes, A. T.; Boeira, S. P.; Prigol, M.; Souza, L. C., Chronic unpredictable mild stress decreases BDNF and NGF levels and Na(+),K(+)-ATPase activity in the hippocampus and prefrontal cortex of mice: antidepressant effect of chrysin. *Neuroscience* **2015,** *289*, 367-80.
39. Krishnan, V.; Han, M. H.; Graham, D. L.; Berton, O.; Renthal, W.; Russo, S. J.; Laplant, Q.; Graham, A.; Lutter, M.; Lagace, D. C.; Ghose, S.; Reister, R.; Tannous, P.; Green, T. A.; Neve, R. L.; Chakravarty, S.; Kumar, A.; Eisch, A. J.; Self, D. W.; Lee, F. S.; Tamminga, C. A.; Cooper, D. C.; Gershenfeld, H. K.; Nestler, E. J., Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* **2007,** *131* (2), 391-404.
40. Golden, S. A.; Covington, H. E., 3rd; Berton, O.; Russo, S. J., A standardized protocol for repeated social defeat stress in mice. *Nat Protoc* **2011,** *6* (8), 1183-91.
41. Lira, A.; Zhou, M.; Castanon, N.; Ansorge, M. S.; Gordon, J. A.; Francis, J. H.; Bradley-Moore, M.; Lira, J.; Underwood, M. D.; Arango, V.; Kung, H. F.; Hofer, M. A.; Hen, R.; Gingrich, J. A., Altered depression-related behaviors and functional changes in the dorsal raphe nucleus of serotonin transporter-deficient mice. *Biol Psychiatry* **2003,** *54* (10), 960-71.
42. Holmes, A.; Yang, R. J.; Murphy, D. L.; Crawley, J. N., Evaluation of antidepressant-related behavioral responses in mice lacking the serotonin transporter. *Neuropsychopharmacology* **2002,** *27* (6), 914-23.
43. Kalueff, A. V.; Olivier, J. D.; Nonkes, L. J.; Homberg, J. R., Conserved role for the serotonin transporter gene in rat and mouse neurobehavioral endophenotypes. *Neurosci Biobehav Rev* **2010,** *34* (3), 373-86.
44. Perona, M. T.; Waters, S.; Hall, F. S.; Sora, I.; Lesch, K. P.; Murphy, D. L.; Caron, M.; Uhl, G. R., Animal models of depression in dopamine, serotonin, and norepinephrine transporter knockout mice: prominent effects of dopamine transporter deletions. *Behav Pharmacol* **2008,** *19* (5-6), 566-74.
45. Lahdesmaki, J.; Sallinen, J.; MacDonald, E.; Kobilka, B. K.; Fagerholm, V.; Scheinin, M., Behavioral and neurochemical characterization of alpha(2A)-adrenergic receptor knockout mice. *Neuroscience* **2002,** *113* (2), 289-99.
46. Schramm, N. L.; McDonald, M. P.; Limbird, L. E., The alpha(2a)-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety. *J Neurosci* **2001,** *21* (13), 4875-82.
47. Muller, M. B.; Holsboer, F., Mice with mutations in the HPA-system as models for symptoms of depression. *Biol Psychiatry* **2006,** *59* (12), 1104-15.
48. Oitzl, M. S.; de Kloet, E. R.; Joels, M.; Schmid, W.; Cole, T. J., Spatial learning deficits in mice with a targeted glucocorticoid receptor gene disruption. *Eur J Neurosci* **1997,** *9* (11), 2284-96.
49. Ridder, S.; Chourbaji, S.; Hellweg, R.; Urani, A.; Zacher, C.; Schmid, W.; Zink, M.; Hortnagl, H.; Flor, H.; Henn, F. A.; Schutz, G.; Gass, P., Mice with genetically altered glucocorticoid receptor expression show altered sensitivity for stress-induced depressive reactions. *J Neurosci* **2005,** *25* (26), 6243-50.
50. Yamada, K.; Iida, R.; Miyamoto, Y.; Saito, K.; Sekikawa, K.; Seishima, M.; Nabeshima, T., Neurobehavioral alterations in mice with a targeted deletion of the tumor necrosis factor-alpha gene: implications for emotional behavior. *J Neuroimmunol* **2000,** *111* (1-2), 131-8.
51. Mesquita, A. R.; Correia-Neves, M.; Roque, S.; Castro, A. G.; Vieira, P.; Pedrosa, J.; Palha, J. A.; Sousa, N., IL-10 modulates depressive-like behavior. *J Psychiatr Res* **2008,** *43* (2), 89-97.
52. Toth, L. A.; Opp, M. R., Cytokine- and microbially induced sleep responses of interleukin-10 deficient mice. *Am J Physiol Regul Integr Comp Physiol* **2001,** *280* (6), R1806-14.
53. Smith, E. M.; Cadet, P.; Stefano, G. B.; Opp, M. R.; Hughes, T. K., Jr., IL-10 as a mediator in the HPA axis and brain. *J Neuroimmunol* **1999,** *100* (1-2), 140-8.
54. Harrison, A. A.; Liem, Y. T.; Markou, A., Fluoxetine combined with a serotonin-1A receptor antagonist reversed reward deficits observed during nicotine and amphetamine withdrawal in rats. *Neuropsychopharmacology* **2001,** *25* (1), 55-71.

55. Paterson, N. E.; Myers, C.; Markou, A., Effects of repeated withdrawal from continuous amphetamine administration on brain reward function in rats. *Psychopharmacology (Berl)* **2000,** *152* (4), 440-6.
56. Cryan, J. F.; Hoyer, D.; Markou, A., Withdrawal from chronic amphetamine induces depressive-like behavioral effects in rodents. *Biol Psychiatry* **2003,** *54* (1), 49-58.
57. Hodes, G. E.; Kana, V.; Menard, C.; Merad, M.; Russo, S. J., Neuroimmune mechanisms of depression. *Nat Neurosci* **2015,** *18* (10), 1386-93.
58. Keifer, J.; Summers, C. H., Putting the "Biology" Back into "Neurobiology": The Strength of Diversity in Animal Model Systems for Neuroscience Research. *Front Syst Neurosci* **2016,** *10*, 69.
59. Kudryavtseva, N. N.; Bondar, N. P.; Avgustinovich, D. F., Effects of repeated experience of aggression on the aggressive motivation and development of anxiety in male mice. *Neurosci Behav Physiol* **2004,** *34* (7), 721-30.
60. Martin, A. L.; Brown, R. E., The lonely mouse: verification of a separation-induced model of depression in female mice. *Behav Brain Res* **2010,** *207* (1), 196-207.
61. Takatsu-Coleman, A. L.; Patti, C. L.; Zanin, K. A.; Zager, A.; Carvalho, R. C.; Borcoi, A. R.; Ceccon, L. M.; Berro, L. F.; Tufik, S.; Andersen, M. L.; Frussa-Filho, R., Short-term social isolation induces depressive-like behaviour and reinstates the retrieval of an aversive task: mood-congruent memory in male mice? *J Psychiatry Neurosci* **2013,** *38* (4), 259-68.
62. Liu, X.; Wu, R.; Tai, F.; Ma, L.; Wei, B.; Yang, X.; Zhang, X.; Jia, R., Effects of group housing on stress induced emotional and neuroendocrine alterations. *Brain Res* **2013,** *1502*, 71-80.
63. Liberzon, I.; Krstov, M.; Young, E. A., Stress-restress: effects on ACTH and fast feedback. *Psychoneuroendocrinology* **1997,** *22* (6), 443-53.
64. Serova, L. I.; Laukova, M.; Alaluf, L. G.; Pucillo, L.; Sabban, E. L., Intranasal neuropeptide Y reverses anxiety and depressive-like behavior impaired by single prolonged stress PTSD model. *Eur Neuropsychopharmacol* **2014,** *24* (1), 142-7.
65. Belzung, C.; Lemoine, M., Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. *Biol Mood Anxiety Disord* **2011,** *1* (1), 9.
66. Sullivan, P. F.; Neale, M. C.; Kendler, K. S., Genetic epidemiology of major depression: review and meta-analysis. *Am J Psychiatry* **2000,** *157* (10), 1552-62.
67. Bosker, F. J.; Hartman, C. A.; Nolte, I. M.; Prins, B. P.; Terpstra, P.; Posthuma, D.; van Veen, T.; Willemsen, G.; DeRijk, R. H.; de Geus, E. J.; Hoogendijk, W. J.; Sullivan, P. F.; Penninx, B. W.; Boomsma, D. I.; Snieder, H.; Nolen, W. A., Poor replication of candidate genes for major depressive disorder using genome-wide association data. *Mol Psychiatry* **2011,** *16* (5), 516-32.
68. Network; Pathway Analysis Subgroup of Psychiatric Genomics, C., Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat Neurosci* **2015,** *18* (2), 199-209.
69. Sallinen, J.; Haapalinna, A.; MacDonald, E.; Viitamaa, T.; Lahdesmaki, J.; Rybnikova, E.; Pelto-Huikko, M.; Kobilka, B. K.; Scheinin, M., Genetic alteration of the alpha2-adrenoceptor subtype c in mice affects the development of behavioral despair and stress-induced increases in plasma corticosterone levels. *Mol Psychiatry* **1999,** *4* (5), 443-52.
70. Bjorklund, M.; Sirvio, J.; Puolivali, J.; Sallinen, J.; Jakala, P.; Scheinin, M.; Kobilka, B. K.; Riekkinen, P., Jr., Alpha2C-adrenoceptor-overexpressing mice are impaired in executing nonspatial and spatial escape strategies. *Mol Pharmacol* **1998,** *54* (3), 569-76.
71. Spielewoy, C.; Roubert, C.; Hamon, M.; Nosten, M.; Betancur, C.; Giros, B., Behavioural disturbances associated with hyperdopaminergia in dopamine-transporter knockout mice. *Behavioural Pharmacology* **2000,** *11* (3-4), 279-290.
72. Holmes, A.; Hollon, T. R.; Gleason, T. C.; Liu, Z.; Dreiling, J.; Sibley, D. R.; Crawley, J. N., Behavioral characterization of dopamine D5 receptor null mutant mice. *Behav Neurosci* **2001,** *115* (5), 1129-44.
73. Filliol, D.; Ghozland, S.; Chluba, J.; Martin, M.; Matthes, H. W.; Simonin, F.; Befort, K.; Gaveriaux-Ruff, C.; Dierich, A.; LeMeur, M.; Valverde, O.; Maldonado, R.; Kieffer, B. L., Mice

deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. *Nat Genet* **2000,** *25* (2), 195-200.
74. Ide, S.; Sora, I.; Ikeda, K.; Minami, M.; Uhl, G. R.; Ishihara, K., Reduced emotional and corticosterone responses to stress in mu-opioid receptor knockout mice. *Neuropharmacology* **2010,** *58* (1), 241-7.
75. Walls, A. B.; Eyjolfsson, E. M.; Smeland, O. B.; Nilsen, L. H.; Schousboe, I.; Schousboe, A.; Sonnewald, U.; Waagepetersen, H. S., Knockout of GAD65 has major impact on synaptic GABA synthesized from astrocyte-derived glutamine. *J Cereb Blood Flow Metab* **2011,** *31* (2), 494-503.
76. Stork, O.; Ji, F. Y.; Kaneko, K.; Stork, S.; Yoshinobu, Y.; Moriya, T.; Shibata, S.; Obata, K., Postnatal development of a GABA deficit and disturbance of neural functions in mice lacking GAD65. *Brain Res* **2000,** *865* (1), 45-58.
77. Miyamoto, Y.; Yamada, K.; Noda, Y.; Mori, H.; Mishina, M.; Nabeshima, T., Lower sensitivity to stress and altered monoaminergic neuronal function in mice lacking the NMDA receptor epsilon 4 subunit. *J Neurosci* **2002,** *22* (6), 2335-42.
78. Cryan, J. F.; Kelly, P. H.; Neijt, H. C.; Sansig, G.; Flor, P. J.; van Der Putten, H., Antidepressant and anxiolytic-like effects in mice lacking the group III metabotropic glutamate receptor mGluR7. *Eur J Neurosci* **2003,** *17* (11), 2409-17.
79. Tordera, R. M.; Totterdell, S.; Wojcik, S. M.; Brose, N.; Elizalde, N.; Lasheras, B.; Del Rio, J., Enhanced anxiety, depressive-like behaviour and impaired recognition memory in mice with reduced expression of the vesicular glutamate transporter 1 (VGLUT1). *Eur J Neurosci* **2007,** *25* (1), 281-90.
80. Garcia-Garcia, A. L.; Elizalde, N.; Matrov, D.; Harro, J.; Wojcik, S. M.; Venzala, E.; Ramirez, M. J.; Del Rio, J.; Tordera, R. M., Increased vulnerability to depressive-like behavior of mice with decreased expression of VGLUT1. *Biol Psychiatry* **2009,** *66* (3), 275-82.
81. Caspi, A.; Sugden, K.; Moffitt, T. E.; Taylor, A.; Craig, I. W.; Harrington, H.; McClay, J.; Mill, J.; Martin, J.; Braithwaite, A.; Poulton, R., Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **2003,** *301* (5631), 386-9.
82. Risch, N.; Herrell, R.; Lehner, T.; Liang, K.-Y.; Eaves, L.; Hoh, J.; Griem, A.; Kovacs, M.; Ott, J.; Merikangas, K. R., Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *Jama* **2009,** *301* (23), 2462-2471.
83. Loftis, J. M.; Huckans, M.; Morasco, B. J., Neuroimmune mechanisms of cytokine-induced depression: current theories and novel treatment strategies. *Neurobiol Dis* **2010,** *37* (3), 519-33.
84. Remus, J. L.; Dantzer, R., Inflammation Models of Depression in Rodents: Relevance to Psychotropic Drug Discovery. *Int J Neuropsychopharmacol* **2016,** *19* (9).
85. Salazar, A.; Gonzalez-Rivera, B. L.; Redus, L.; Parrott, J. M.; O'Connor, J. C., Indoleamine 2,3-dioxygenase mediates anhedonia and anxiety-like behaviors caused by peripheral lipopolysaccharide immune challenge. *Horm Behav* **2012,** *62* (3), 202-9.
86. Biesmans, S.; Matthews, L. J.; Bouwknecht, J. A.; De Haes, P.; Hellings, N.; Meert, T. F.; Nuydens, R.; Ver Donck, L., Systematic Analysis of the Cytokine and Anhedonia Response to Peripheral Lipopolysaccharide Administration in Rats. *Biomed Res Int* **2016,** *2016*, 9085273.
87. Walker, F. R.; Knott, B.; Hodgson, D. M., Neonatal endotoxin exposure modifies the acoustic startle response and circulating levels of corticosterone in the adult rat but only following acute stress. *J Psychiatr Res* **2008,** *42* (13), 1094-103.
88. Granger, D. A.; Hood, K. E.; Dreschel, N. A.; Sergeant, E.; Likos, A., Developmental effects of early immune stress on aggressive, socially reactive, and inhibited behaviors. *Dev Psychopathol* **2001,** *13* (3), 599-610.
89. Majidi, J.; Kosari-Nasab, M.; Salari, A. A., Developmental minocycline treatment reverses the effects of neonatal immune activation on anxiety- and depression-like behaviors, hippocampal inflammation, and HPA axis activity in adult mice. *Brain Res Bull* **2016,** *120*, 1-13.
90. Gibney, S. M.; McGuinness, B.; Prendergast, C.; Harkin, A.; Connor, T. J., Poly I:C-induced activation of the immune response is accompanied by depression and anxiety-like behaviours, kynurenine pathway activation and reduced BDNF expression. *Brain Behav Immun* **2013,** *28*, 170-81.

91. Kaneko, N.; Kudo, K.; Mabuchi, T.; Takemoto, K.; Fujimaki, K.; Wati, H.; Iguchi, H.; Tezuka, H.; Kanba, S., Suppression of cell proliferation by interferon-alpha through interleukin-1 production in adult rat dentate gyrus. *Neuropsychopharmacology* **2006,** *31* (12), 2619-26.
92. Orsal, A. S.; Blois, S. M.; Bermpohl, D.; Schaefer, M.; Coquery, N., Administration of interferon-alpha in mice provokes peripheral and central modulation of immune cells, accompanied by behavioral effects. *Neuropsychobiology* **2008,** *58* (3-4), 211-22.
93. Kentner, A. C.; James, J. S.; Miguelez, M.; Bielajew, C., Investigating the hedonic effects of interferon-alpha on female rats using brain-stimulation reward. *Behav Brain Res* **2007,** *177* (1), 90-9.
94. Moreau, M.; Andre, C.; O'Connor, J. C.; Dumich, S. A.; Woods, J. A.; Kelley, K. W.; Dantzer, R.; Lestage, J.; Castanon, N., Inoculation of Bacillus Calmette-Guerin to mice induces an acute episode of sickness behavior followed by chronic depressive-like behavior. *Brain Behav Immun* **2008,** *22* (7), 1087-95.
95. O'Connor, J. C.; Lawson, M. A.; Andre, C.; Briley, E. M.; Szegedi, S. S.; Lestage, J.; Castanon, N.; Herkenham, M.; Dantzer, R.; Kelley, K. W., Induction of IDO by bacille Calmette-Guerin is responsible for development of murine depressive-like behavior. *J Immunol* **2009,** *182* (5), 3202-12.
96. Renoir, T.; Pang, T. Y.; Lanfumey, L., Drug withdrawal-induced depression: serotonergic and plasticity changes in animal models. *Neurosci Biobehav Rev* **2012,** *36* (1), 696-726.
97. Zabegalov, K. N.; Kolesnikova, T. O.; Khatsko, S. L.; Volgin, A. D.; Yakovlev, O. A.; Amstislavskaya, T. G.; Alekseeva, P. A.; Meshalkina, D. A.; Friend, A. J.; Bao, W.; Demin, K. A.; Gainetdinov, R. R.; Kalueff, A. V., Understanding antidepressant discontinuation syndrome (ADS) through preclinical experimental models. *Eur J Pharmacol* **2018,** *829*, 129-140.
98. Güdük, M.; Erensoy, İ. Y.; Ersümer, F., Mania/hypomania associated with antidepressant discontinuation. *Düşünen Adam: The Journal of Psychiatry and Neurological Sciences* **2013,** *26* (3), 303-306.
99. Merali, Z.; Brennan, K.; Brau, P.; Anisman, H., Dissociating anorexia and anhedonia elicited by interleukin-1beta: antidepressant and gender effects on responding for "free chow" and "earned" sucrose intake. *Psychopharmacology (Berl)* **2003,** *165* (4), 413-8.
100. Sammut, S.; Bethus, I.; Goodall, G.; Muscat, R., Antidepressant reversal of interferon-alpha-induced anhedonia. *Physiol Behav* **2002,** *75* (5), 765-72.
101. Makino, M.; Kitano, Y.; Komiyama, C.; Hirohashi, M.; Kohno, M.; Moriyama, M.; Takasuna, K., Human interferon-alpha induces immobility in the mouse forced swimming test: involvement of the opioid system. *Brain Res* **2000,** *852* (2), 482-4.
102. Plata-Salaman, C. R.; Oomura, Y.; Kai, Y., Tumor necrosis factor and interleukin-1 beta: suppression of food intake by direct action in the central nervous system. *Brain Res* **1988,** *448* (1), 106-14.
103. El Yacoubi, M.; Bouali, S.; Popa, D.; Naudon, L.; Leroux-Nicollet, I.; Hamon, M.; Costentin, J.; Adrien, J.; Vaugeois, J. M., Behavioral, neurochemical, and electrophysiological characterization of a genetic mouse model of depression. *Proc Natl Acad Sci U S A* **2003,** *100* (10), 6227-32.
104. Krueger, J. M.; Majde, J. A., Humoral links between sleep and the immune system: research issues. *Ann N Y Acad Sci* **2003,** *992*, 9-20.
105. Dantzer, R.; Bluthe, R. M.; Kelley, K. W., Androgen-dependent vasopressinergic neurotransmission attenuates interleukin-1-induced sickness behavior. *Brain Res* **1991,** *557* (1-2), 115-20.
106. Wood, L. J.; Nail, L. M.; Gilster, A.; Winters, K. A.; Elsea, C. R., Cancer chemotherapy-related symptoms: evidence to suggest a role for proinflammatory cytokines. *Oncol Nurs Forum* **2006,** *33* (3), 535-42.
107. Bonaccorso, S.; Maier, S. F.; Meltzer, H. Y.; Maes, M., Behavioral changes in rats after acute, chronic and repeated administration of interleukin-1beta: relevance for affective disorders. *J Affect Disord* **2003,** *77* (2), 143-8.

108. Song, C.; Horrobin, D. F.; Leonard, B. E., The comparison of changes in behavior, neurochemistry, endocrine, and immune functions after different routes, doses and durations of administrations of IL-1beta in rats. *Pharmacopsychiatry* **2006,** *39* (3), 88-99.
109. Nonogaki, K.; Abdallah, L.; Goulding, E. H.; Bonasera, S. J.; Tecott, L. H., Hyperactivity and reduced energy cost of physical activity in serotonin 5-HT(2C) receptor mutant mice. *Diabetes* **2003,** *52* (2), 315-20.
110. Ballard, T. M.; Pauly-Evers, M.; Higgins, G. A.; Ouagazzal, A. M.; Mutel, V.; Borroni, E.; Kemp, J. A.; Bluethmann, H.; Kew, J. N., Severe impairment of NMDA receptor function in mice carrying targeted point mutations in the glycine binding site results in drug-resistant nonhabituating hyperactivity. *J Neurosci* **2002,** *22* (15), 6713-23.
111. Cheeta, S.; Ruigt, G.; van Proosdij, J.; Willner, P., Changes in sleep architecture following chronic mild stress. *Biol Psychiatry* **1997,** *41* (4), 419-27.
112. Steru, L.; Chermat, R.; Thierry, B.; Simon, P., The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology (Berl)* **1985,** *85* (3), 367-70.
113. O'Leary, O. F.; Cryan, J. F., Towards translational rodent models of depression. *Cell Tissue Res* **2013,** *354* (1), 141-53.
114. Porsolt, R. D.; Le Pichon, M.; Jalfre, M., Depression: a new animal model sensitive to antidepressant treatments. *Nature* **1977,** *266* (5604), 730-2.
115. Lucki, I., The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. *Behav Pharmacol* **1997,** *8* (6-7), 523-32.
116. Porsolt, R. D.; Bertin, A.; Jalfre, M., "Behavioural despair" in rats and mice: strain differences and the effects of imipramine. *Eur J Pharmacol* **1978,** *51* (3), 291-4.
117. Porsolt, R. D.; Bertin, A.; Jalfre, M., Behavioral despair in mice: a primary screening test for antidepressants. *Arch Int Pharmacodyn Ther* **1977,** *229* (2), 327-36.
118. Steru, L.; Chermat, R.; Thierry, B.; Mico, J. A.; Lenegre, A.; Steru, M.; Simon, P.; Porsolt, R. D., The automated Tail Suspension Test: a computerized device which differentiates psychotropic drugs. *Prog Neuropsychopharmacol Biol Psychiatry* **1987,** *11* (6), 659-71.
119. Commons, K. G.; Cholanians, A. B.; Babb, J. A.; Ehlinger, D. G., The Rodent Forced Swim Test Measures Stress-Coping Strategy, Not Depression-like Behavior. *ACS Chem Neurosci* **2017,** *8* (5), 955-960.
120. Nelson, E. E.; Winslow, J. T., Non-human primates: model animals for developmental psychopathology. *Neuropsychopharmacology* **2009,** *34* (1), 90.
121. Barr, C. S.; Newman, T. K.; Becker, M. L.; Parker, C. C.; Champoux, M.; Lesch, K.; Goldman, D.; Suomi, S.; Higley, J., The utility of the non-human primate model for studying gene by environment interactions in behavioral research. *Genes, Brain and Behavior* **2003,** *2* (6), 336-340.
122. Suomi, S.; Harlow, H., Production and alleviation of depressive behaviors in monkeys. WH Freeman, San Francisco: 1977; Vol. 131.
123. Harro, J., Animal models of depression vulnerability. *Curr Top Behav Neurosci* **2013,** *14*, 29-54.
124. Suomi, S. J., Repetitive peer separation of young monkeys: Effects of vertical chamber confinement during separations. *Journal of abnormal psychology* **1973,** *81* (1), 1.
125. Worlein, J. M., Nonhuman primate models of depression: effects of early experience and stress. *ILAR journal* **2014,** *55* (2), 259-273.
126. Vellucci, S. V., Primate social behavior—anxiety or depression? *Pharmacology & therapeutics* **1990,** *47* (2), 167-180.
127. McKinney, W.; Moran, E.; Kramer, G., Effects of drugs on the response to social separation in rhesus monkeys. In *Hormones, Drugs and Social Behavior in Primates*, Spectrum Publications New York: 1983; pp 249-270.
128. Suomi, S. J.; Seaman, S. F.; Lewis, J. K.; DeLizio, R. D.; McKinney, W. T., Effects of imipramine treatment of separation-induced social disorders in rhesus monkeys. *Archives of General Psychiatry* **1978,** *35* (3), 321-325.
129. Rasmussen, K. L.; Reite, M., Loss-induced depression in an adult macaque monkey. *The American journal of psychiatry* **1982**.

130. Kraemer, G. W.; Lin, D. H.; Moran, E. C.; McKinney, W. T., Effects of alcohol on the despair response to peer separation in rhesus monkeys. *Psychopharmacology* **1981,** *73* (4), 307-310.
131. Redmond, D. E.; Maas, J. W.; Kling, A.; Dekirmenjian, H., Changes in primate social behavior after treatment with alpha-methyl-para-tyrosine. *Psychosomatic medicine* **1971**.
132. Kalidindi, A.; Kelly, S. D.; Singleton, K. S.; Guzman, D.; Merrill, L.; Willard, S. L.; Shively, C. A.; Neigh, G. N., Reduced marker of vascularization in the anterior hippocampus in a female monkey model of depression. *Physiology & behavior* **2017,** *172*, 12-15.
133. Clarke, A. S.; Hedeker, D. R.; Ebert, M. H.; Schmidt, D. E.; McKinney, W. T.; Kraemer, G. W., Rearing experience and biogenic amine activity in infant rhesus monkeys. *Biological Psychiatry* **1996,** *40* (5), 338-352.
134. Clarke, A. S.; Ebert, M. H.; Schmidt, D. E.; McKinney, W. T.; Kraemer, G. W., Biogenic amine activity in response to fluoxetine and desipramine in differentially reared rhesus monkeys. *Biological psychiatry* **1999,** *46* (2), 221-228.
135. Kraemer, G. W.; Ebert, M. H.; Lake, C. R.; McKinney, W. T., Amphetamine challenge: effects in previously isolated rhesus monkeys and implications for animal models of schizophrenia. *Progress in clinical and biological research* **1983,** *131*, 199-218.
136. Kraemer, G. W.; Ebert, M. H.; Lake, C. R.; McKinney, W. T., Hypersensitivity to d-amphetamine several years after early social deprivation in rhesus monkeys. *Psychopharmacology* **1984,** *82* (3), 266-271.
137. Higley, J. D.; Suomi, S. J.; Linnoila, M., A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. *Biological psychiatry* **1992,** *32* (2), 127-145.
138. Winslow, J. T., Neuropeptides and non-human primate social deficits associated with pathogenic rearing experience. *International Journal of Developmental Neuroscience* **2005,** *23* (2-3), 245-251.
139. Kraemer, G. W.; McKinney, W. T., Interactions of pharmacological agents which alter biogenic amine metabolism and depression: An analysis of contributing factors within a primate model of depression. *Journal of Affective Disorders* **1979,** *1* (1), 33-54.
140. Zhang, Z.-y.; Mao, Y.; Feng, X.-l.; Zheng, N.; Lü, L.-b.; Ma, Y.-y.; Qin, D.-d.; Hu, X.-t., Early adversity contributes to chronic stress induced depression-like behavior in adolescent male rhesus monkeys. *Behavioural brain research* **2016,** *306*, 154-159.
141. Felger, J. C.; Alagbe, O.; Hu, F.; Mook, D.; Freeman, A. A.; Sanchez, M. M.; Kalin, N. H.; Ratti, E.; Nemeroff, C. B.; Miller, A. H., Effects of interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. *Biological psychiatry* **2007,** *62* (11), 1324-1333.
142. Meshalkina, D. A.; Kysil, E. V.; Warnick, J. E.; Demin, K. A.; Kalueff, A. V., Adult zebrafish in CNS disease modeling: a tank that's half-full, not half-empty, and still filling. *Lab Anim (NY)* **2017,** *46* (10), 378-387.
143. Demin, K. A.; Meshalkina, D. A.; Kysil, E. V.; Antonova, K. A.; Volgin, A. D.; Yakovlev, O. A.; Alekseeva, P. A.; Firuleva, M. M.; Lakstygal, A. M.; de Abreu, M. S.; Barcellos, L. J. G.; Bao, W.; Friend, A. J.; Amstislavskaya, T. G.; Rosemberg, D. B.; Musienko, P. E.; Song, C.; Kalueff, A. V., Zebrafish models relevant to studying central opioid and endocannabinoid systems. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **2018**.
144. Stewart, A. M.; Ullmann, J. F.; Norton, W. H.; Parker, M. O.; Brennan, C. H.; Gerlai, R.; Kalueff, A. V., Molecular psychiatry of zebrafish. *Molecular Psychiatry* **2015,** *20* (1), 2-17.
145. Kalueff, A. V.; Stewart, A. M.; Gerlai, R., Zebrafish as an emerging model for studying complex brain disorders. *Trends Pharmacol Sci* **2014,** *35* (2), 63-75.
146. Khan, K. M.; Collier, A. D.; Meshalkina, D. A.; Kysil, E. V.; Khatsko, S. L.; Kolesnikova, T.; Morzherin, Y. Y.; Warnick, J. E.; Kalueff, A. V.; Echevarria, D. J., Zebrafish models in neuropsychopharmacology and CNS drug discovery. *Br J Pharmacol* **2017,** *174* (13), 1925-1944.
147. de Abreu, M. S.; Friend, A. J.; Demin, K. A.; Amstislavskaya, T. G.; Bao, W.; Kalueff, A. V., Zebrafish models: do we have valid paradigms for depression? *Journal of pharmacological and toxicological methods* **2018**.

148. Manuel, R.; Gorissen, M.; Zethof, J.; Ebbesson, L. O.; van de Vis, H.; Flik, G.; van den Bos, R., Unpredictable chronic stress decreases inhibitory avoidance learning in Tuebingen long-fin zebrafish: stronger effects in the resting phase than in the active phase. *J Exp Biol* **2014,** *217* (Pt 21), 3919-28.
149. Chakravarty, S.; Reddy, B. R.; Sudhakar, S. R.; Saxena, S.; Das, T.; Meghah, V.; Brahmendra Swamy, C. V.; Kumar, A.; Idris, M. M., Chronic unpredictable stress (CUS)-induced anxiety and related mood disorders in a zebrafish model: altered brain proteome profile implicates mitochondrial dysfunction. *PLoS One* **2013,** *8* (5), e63302.
150. Fulcher, N.; Tran, S.; Shams, S.; Chatterjee, D.; Gerlai, R., Neurochemical and Behavioral Responses to Unpredictable Chronic Mild Stress Following Developmental Isolation: The Zebrafish as a Model for Major Depression. *Zebrafish* **2017,** *14* (1), 23-34.
151. Song, C.; Liu, B. P.; Zhang, Y. P.; Peng, Z.; Wang, J.; Collier, A. D.; Echevarria, D. J.; Savelieva, K. V.; Lawrence, R. F.; Rex, C. S.; Meshalkina, D. A.; Kalueff, A. V., Modeling consequences of prolonged strong unpredictable stress in zebrafish: Complex effects on behavior and physiology. *Prog Neuropsychopharmacol Biol Psychiatry* **2018,** *81*, 384-394.
152. Pavlidis, M.; Theodoridi, A.; Tsalafouta, A., Neuroendocrine regulation of the stress response in adult zebrafish, Danio rerio. *Prog Neuropsychopharmacol Biol Psychiatry* **2015,** *60*, 121-31.
153. Zimmermann, F. F.; Altenhofen, S.; Kist, L. W.; Leite, C. E.; Bogo, M. R.; Cognato, G. P.; Bonan, C. D., Unpredictable Chronic Stress Alters Adenosine Metabolism in Zebrafish Brain. *Mol Neurobiol* **2016,** *53* (4), 2518-28.
154. McCammon, J. M.; Sive, H., Addressing the Genetics of Human Mental Health Disorders in Model Organisms. *Annu Rev Genomics Hum Genet* **2015,** *16*, 173-97.
155. Mann, J. J., Role of the serotonergic system in the pathogenesis of major depression and suicidal behavior. *Neuropsychopharmacology* **1999,** *21* (2), 99S-105S.
156. Rapport, M. M.; Green, A. A.; Page, I. H., Crystalline serotonin. *Science* **1948,** *108* (2804), 329-330.
157. Popa, D.; Lena, C.; Alexandre, C.; Adrien, J., Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior. *J Neurosci* **2008,** *28* (14), 3546-54.
158. Vogel, G.; Neill, D.; Kors, D.; Hagler, M., REM sleep abnormalities in a new animal model of endogenous depression. *Neurosci Biobehav Rev* **1990,** *14* (1), 77-83.
159. Ramboz, S.; Oosting, R.; Amara, D. A.; Kung, H. F.; Blier, P.; Mendelsohn, M.; Mann, J. J.; Brunner, D.; Hen, R., Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. *Proc Natl Acad Sci U S A* **1998,** *95* (24), 14476-81.
160. Mayorga, A. J.; Dalvi, A.; Page, M. E.; Zimov-Levinson, S.; Hen, R.; Lucki, I., Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B) receptor mutant mice. *J Pharmacol Exp Ther* **2001,** *298* (3), 1101-7.
161. Hepgul, N.; Cattaneo, A.; Zunszain, P. A.; Pariante, C. M., Depression pathogenesis and treatment: what can we learn from blood mRNA expression? *BMC medicine* **2013,** *11* (1), 28.
162. Cattaneo, A.; Gennarelli, M.; Uher, R.; Breen, G.; Farmer, A.; Aitchison, K. J.; Craig, I. W.; Anacker, C.; Zunsztain, P. A.; McGuffin, P., Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology* **2013,** *38* (3), 377.
163. Katzav, A.; Solodeev, I.; Brodsky, O.; Chapman, J.; Pick, C. G.; Blank, M.; Zhang, W.; Reichlin, M.; Shoenfeld, Y., Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. *Arthritis Rheum* **2007,** *56* (3), 938-48.
164. Köhler, O.; Benros, M. E.; Nordentoft, M.; Farkouh, M. E.; Iyengar, R. L.; Mors, O.; Krogh, J., Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA psychiatry* **2014,** *71* (12), 1381-1391.
165. O'connor, J.; Lawson, M.; Andre, C.; Moreau, M.; Lestage, J.; Castanon, N.; Kelley, K.; Dantzer, R., Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2, 3-dioxygenase activation in mice. *Molecular psychiatry* **2009,** *14* (5), 511.

166. Miller, A. H.; Maletic, V.; Raison, C. L., Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological psychiatry* **2009,** *65* (9), 732-741.
167. Rajkowska, G.; Stockmeier, C. A., Astrocyte pathology in major depressive disorder: insights from human postmortem brain tissue. *Curr Drug Targets* **2013,** *14* (11), 1225-36.
168. Rajkowska, G.; Miguel-Hidalgo, J., Gliogenesis and glial pathology in depression. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)* **2007,** *6* (3), 219-233.
169. Peuchen, S.; Bolaños, J. P.; Heales, S. J.; Almeida, A.; Duchen, M. R.; Clark, J. B., Interrelationships between astrocyte function, oxidative stress and antioxidant status within the central nervous system. *Prog Neurobiol* **1997,** *52* (4), 261-281.
170. Anderson, C. M.; Nedergaard, M., Astrocyte-mediated control of cerebral microcirculation. *Trends in neurosciences* **2003,** *26* (7), 340-344.
171. Benarroch, E. E. In *Neuron-astrocyte interactions: partnership for normal function and disease in the central nervous system*, Mayo Clinic Proceedings, Elsevier: 2005; pp 1326-1338.
172. Braun, K.; Antemano, R.; Helmeke, C.; Büchner, M.; Poeggel, G., Juvenile separation stress induces rapid region-and layer-specific changes in S100ß-and glial fibrillary acidic protein–immunoreactivity in astrocytes of the rodent medial prefrontal cortex. *Neuroscience* **2009,** *160* (3), 629-638.
173. Araya-Callís, C.; Hiemke, C.; Abumaria, N.; Flugge, G., Chronic psychosocial stress and citalopram modulate the expression of the glial proteins GFAP and NDRG2 in the hippocampus. *Psychopharmacology* **2012,** *224* (1), 209-222.
174. Leventopoulos, M.; Rüedi-Bettschen, D.; Knuesel, I.; Feldon, J.; Pryce, C. R.; Opacka-Juffry, J., Long-term effects of early life deprivation on brain glia in Fischer rats. *Brain research* **2007,** *1142*, 119-126.
175. Banasr, M.; Duman, R. S., Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biological psychiatry* **2008,** *64* (10), 863-870.
176. Lee, Y.; Son, H.; Kim, G.; Kim, S.; Lee, D. H.; Roh, G. S.; Kang, S. S.; Cho, G. J.; Choi, W. S.; Kim, H. J., Glutamine deficiency in the prefrontal cortex increases depressive-like behaviours in male mice. *Journal of psychiatry & neuroscience: JPN* **2013,** *38* (3), 183.
177. Cryan, J. F.; Dinan, T. G., Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nature reviews neuroscience* **2012,** *13* (10), 701.
178. Mayer, E. A., Gut feelings: the emerging biology of gut–brain communication. *Nature Reviews Neuroscience* **2011,** *12* (8), 453.
179. Selkrig, J.; Wong, P.; Zhang, X.; Pettersson, S., Metabolic tinkering by the gut microbiome: implications for brain development and function. *Gut microbes* **2014,** *5* (3), 369-380.
180. Bercik, P.; Denou, E.; Collins, J.; Jackson, W.; Lu, J.; Jury, J.; Deng, Y.; Blennerhassett, P.; Macri, J.; McCoy, K. D., The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology* **2011,** *141* (2), 599-609. e3.
181. Zheng, P.; Zeng, B.; Zhou, C.; Liu, M.; Fang, Z.; Xu, X.; Zeng, L.; Chen, J.; Fan, S.; Du, X., Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Molecular psychiatry* **2016,** *21* (6), 786.
182. Heijtz, R. D.; Wang, S.; Anuar, F.; Qian, Y.; Björkholm, B.; Samuelsson, A.; Hibberd, M. L.; Forssberg, H.; Pettersson, S., Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences* **2011,** *108* (7), 3047-3052.
183. Bravo, J. A.; Forsythe, P.; Chew, M. V.; Escaravage, E.; Savignac, H. M.; Dinan, T. G.; Bienenstock, J.; Cryan, J. F., Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences* **2011**, 201102999.
184. Savignac, H.; Kiely, B.; Dinan, T.; Cryan, J., B ifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. *Neurogastroenterology & Motility* **2014,** *26* (11), 1615-1627.
185. Savignac, H.; Tramullas, M.; Kiely, B.; Dinan, T.; Cryan, J., Bifidobacteria modulate cognitive processes in an anxious mouse strain. *Behavioural brain research* **2015,** *287*, 59-72.

186. Dinan, T. G.; Stanton, C.; Cryan, J. F., Psychobiotics: a novel class of psychotropic. *Biological psychiatry* **2013,** *74* (10), 720-726.
187. Bornstein, S. R.; Schuppenies, A.; Wong, M. L.; Licinio, J., Approaching the shared biology of obesity and depression: the stress axis as the locus of gene-environment interactions. *Mol Psychiatry* **2006,** *11* (10), 892-902.
188. Purcell, R. H.; Sun, B.; Pass, L. L.; Power, M. L.; Moran, T. H.; Tamashiro, K. L., Maternal stress and high-fat diet effect on maternal behavior, milk composition, and pup ingestive behavior. *Physiol Behav* **2011,** *104* (3), 474-9.
189. Sharma, S.; Fulton, S., Diet-induced obesity promotes depressive-like behaviour that is associated with neural adaptations in brain reward circuitry. *Int J Obes (Lond)* **2013,** *37* (3), 382-9.
190. Dong, C.; Sanchez, L. E.; Price, R. A., Relationship of obesity to depression: a family-based study. *Int J Obes Relat Metab Disord* **2004,** *28* (6), 790-5.
191. Simon, G. E.; Von Korff, M.; Saunders, K.; Miglioretti, D. L.; Crane, P. K.; van Belle, G.; Kessler, R. C., Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* **2006,** *63* (7), 824-30.
192. Petrak, F.; Röhrig, B.; Ismail, K., Depression and Diabetes. In *Endotext [Internet]*, MDText. com, Inc.: 2018.
193. Sakimura, K.; Maekawa, T.; Sasagawa, K.; Ishii, Y.; Kume, S. i.; Ohta, T., Depression-related behavioural and neuroendocrine changes in the Spontaneously Diabetic Torii (SDT) fatty rat, an animal model of Type 2 Diabetes Mellitus. *Clinical and Experimental Pharmacology and Physiology* **2018**.
194. Aswar, U.; Chepurwar, S.; Shintre, S.; Aswar, M., Telmisartan attenuates diabetes induced depression in rats. *Pharmacological reports* **2017,** *69* (2), 358-364.
195. Robinson, K. S.; Stewart, A. M.; Cachat, J.; Landsman, S.; Gebhardt, M.; Kalueff, A. V., Psychopharmacological effects of acute exposure to kynurenic acid (KYNA) in zebrafish. *Pharmacol Biochem Behav* **2013,** *108*, 54-60.
196. Dos Santos, M. M.; de Macedo, G. T.; Prestes, A. S.; Loro, V. L.; Heidrich, G. M.; Picoloto, R. S.; Rosemberg, D. B.; Barbosa, N. V., Hyperglycemia elicits anxiety-like behaviors in zebrafish: Protective role of dietary diphenyl diselenide. *Prog Neuropsychopharmacol Biol Psychiatry* **2018,** *85*, 128-135.
197. Willner, P.; Belzung, C., Treatment-resistant depression: are animal models of depression fit for purpose? *Psychopharmacology* **2015,** *232* (19), 3473-3495.
198. Anreiter, I.; Sokolowski, H. M.; Sokolowski, M. B., Gene–Environment Interplay and Individual Differences in Behavior. *Mind, Brain, and Education* **2017,** *0* (0).
199. Perani, C. V.; Slattery, D. A., Using animal models to study post-partum psychiatric disorders. *British Journal of Pharmacology* **2014,** *171* (20), 4539-4555.
200. Lavi-Avnon, Y.; Weller, A.; Finberg, J. P.; Gispan-Herman, I.; Kinor, N.; Stern, Y.; Schroeder, M.; Gelber, V.; Bergman, S. Y.; Overstreet, D. H.; Yadid, G., The reward system and maternal behavior in an animal model of depression: a microdialysis study. *Psychopharmacology (Berl)* **2008,** *196* (2), 281-91.
201. Petersen, A.; Wortwein, G.; Gruber, S. H.; Mathe, A. A., Escitalopram reduces increased hippocampal cytogenesis in a genetic rat depression model. *Neurosci Lett* **2008,** *436* (3), 305-8.
202. Weiss, J. M.; Cierpial, M. A.; West, C. H., Selective breeding of rats for high and low motor activity in a swim test: toward a new animal model of depression. *Pharmacol Biochem Behav* **1998,** *61* (1), 49-66.
203. West, C. H.; Weiss, J. M., A selective test for antidepressant treatments using rats bred for stress-induced reduction of motor activity in the swim test. *Psychopharmacology (Berl)* **2005,** *182* (1), 9-23.
204. Okamoto, K.; Aoki, K., Development of a strain of spontaneously hypertensive rats. *Jpn Circ J* **1963,** *27*, 282-93.
205. Armario, A.; Gavalda, A.; Marti, J., Comparison of the behavioural and endocrine response to forced swimming stress in five inbred strains of rats. *Psychoneuroendocrinology* **1995,** *20* (8), 879-90.

206. El Yacoubi, M.; Vaugeois, J. M., Genetic rodent models of depression. *Curr Opin Pharmacol* **2007,** *7* (1), 3-7.
207. Popa, D.; El Yacoubi, M.; Vaugeois, J. M.; Hamon, M.; Adrien, J., Homeostatic regulation of sleep in a genetic model of depression in the mouse: effects of muscarinic and 5-HT1A receptor activation. *Neuropsychopharmacology* **2006,** *31* (8), 1637-46.
208. Bougarel, L.; Guitton, J.; Zimmer, L.; Vaugeois, J. M.; El Yacoubi, M., Behaviour of a genetic mouse model of depression in the learned helplessness paradigm. *Psychopharmacology (Berl)* **2011,** *215* (3), 595-605.
209. Shumake, J.; Poremba, A.; Edwards, E.; Gonzalez-Lima, F., Congenital helpless rats as a genetic model for cortex metabolism in depression. *Neuroreport* **2000,** *11* (17), 3793-8.
210. Overstreet, D. H.; Rezvani, A. H.; Knapp, D. J.; Crews, F. T.; Janowsky, D. S., Further selection of rat lines differing in 5-HT-1A receptor sensitivity: behavioral and functional correlates. *Psychiatr Genet* **1996,** *6* (3), 107-17.
211. Commissaris, R. L.; Ardayfio, P. A.; McQueen, D. A.; Gilchrist, G. A., 3rd; Overstreet, D. H., Conflict behavior and the effects of 8-OHDPAT treatment in rats selectively bred for differential 5-HT(1A)-induced hypothermia. *Pharmacol Biochem Behav* **2000,** *67* (1), 199-205.
212. File, S. E.; Ouagazzal, A. M.; Gonzalez, L. E.; Overstreet, D. H., Chronic fluoxetine in tests of anxiety in rat lines selectively bred for differential 5-HT1A receptor function. *Pharmacol Biochem Behav* **1999,** *62* (4), 695-701.
213. Kromer, S. A.; Kessler, M. S.; Milfay, D.; Birg, I. N.; Bunck, M.; Czibere, L.; Panhuysen, M.; Putz, B.; Deussing, J. M.; Holsboer, F.; Landgraf, R.; Turck, C. W., Identification of glyoxalase-I as a protein marker in a mouse model of extremes in trait anxiety. *J Neurosci* **2005,** *25* (17), 4375-84.
214. Bayne, K.; Wurbel, H., The impact of environmental enrichment on the outcome variability and scientific validity of laboratory animal studies. *Revue scientifique et technique (International Office of Epizootics)* **2014,** *33* (1), 273-80.
215. Nader, J.; Claudia, C.; El Rawas, R.; Favot, L.; Jaber, M.; Thiriet, N.; Solinas, M., Loss of environmental enrichment increases vulnerability to cocaine addiction. *Neuropsychopharmacology* **2012,** *37* (7), 1579.
216. Sáenz, J. C. B.; Villagra, O. R.; Trías, J. F., Factor analysis of forced swimming test, sucrose preference test and open field test on enriched, social and isolated reared rats. *Behavioural brain research* **2006,** *169* (1), 57-65.
217. Hattori, S.; Hashimoto, R.; Miyakawa, T.; Yamanaka, H.; Maeno, H.; Wada, K.; Kunugi, H., Enriched environments influence depression-related behavior in adult mice and the survival of newborn cells in their hippocampi. *Behavioural brain research* **2007,** *180* (1), 69-76.
218. Koh, S.; Magid, R.; Chung, H.; Stine, C. D.; Wilson, D. N., Depressive behavior and selective downregulation of serotonin receptor expression after early-life seizures: reversal by environmental enrichment. *Epilepsy & Behavior* **2007,** *10* (1), 26-31.
219. Wright, D.; Nakamichi, R.; Krause, J.; Butlin, R. K., QTL analysis of behavioral and morphological differentiation between wild and laboratory zebrafish (Danio rerio). *Behavior genetics* **2006,** *36* (2), 271.
220. Wright, D.; Rimmer, L. B.; Pritchard, V. L.; Krause, J.; Butlin, R. K., Inter and intra-population variation in shoaling and boldness in the zebrafish (Danio rerio). *Naturwissenschaften* **2003,** *90* (8), 374-7.
221. Dugatkin, L.; McCall, M.; Gregg, R.; Cavanaugh, A.; Christensen, C.; Unseld, M., Zebrafish (Danio rerio) exhibit individual differences in risk-taking behavior during predator inspection. *Ethology Ecology & Evolution* **2005,** *17* (1), 77-81.
222. Moretz, J. A.; Martins, E. P.; Robison, B. D., Behavioral syndromes and the evolution of correlated behavior in zebrafish. *Behavioral ecology* **2007,** *18* (3), 556-562.
223. Volgin, A. D.; Yakovlev, O. V.; Demin, K. A.; Abreu, M. S. d.; Rosemberg, D. B.; Meshalkina, D. A.; Alekseeva, P. A.; Friend, A. J.; Amstislavskaya, T. G.; Kalueff, A. V., Understanding the Role of Environmental Enrichment in Zebrafish Neurobehavioral Models. *Zebrafish* **2018**.

224. Mathew, S. J.; Shah, A.; Lapidus, K.; Clark, C.; Jarun, N.; Ostermeyer, B.; Murrough, J. W., Ketamine for treatment-resistant unipolar depression. *CNS drugs* **2012,** *26* (3), 189-204.
225. Berman, R. M.; Cappiello, A.; Anand, A.; Oren, D. A.; Heninger, G. R.; Charney, D. S.; Krystal, J. H., Antidepressant effects of ketamine in depressed patients. *Biological psychiatry* **2000,** *47* (4), 351-354.
226. Zarate, C. A.; Singh, J. B.; Carlson, P. J.; Brutsche, N. E.; Ameli, R.; Luckenbaugh, D. A.; Charney, D. S.; Manji, H. K., A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of general psychiatry* **2006,** *63* (8), 856-864.
227. Ibrahim, L.; Diazgranados, N.; Luckenbaugh, D. A.; Machado-Vieira, R.; Baumann, J.; Mallinger, A. G.; Zarate Jr, C. A., Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **2011,** *35* (4), 1155-1159.
228. Murrough, J. W.; Iosifescu, D. V.; Chang, L. C.; Al Jurdi, R. K.; Green, C. E.; Perez, A. M.; Iqbal, S.; Pillemer, S.; Foulkes, A.; Shah, A., Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *American Journal of Psychiatry* **2013,** *170* (10), 1134-1142.
229. Diazgranados, N.; Ibrahim, L.; Brutsche, N. E.; Newberg, A.; Kronstein, P.; Khalife, S.; Kammerer, W. A.; Quezado, Z.; Luckenbaugh, D. A.; Salvadore, G., A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of general psychiatry* **2010,** *67* (8), 793-802.
230. Burgdorf, J.; Zhang, X.-l.; Nicholson, K. L.; Balster, R. L.; Leander, J. D.; Stanton, P. K.; Gross, A. L.; Kroes, R. A.; Moskal, J. R., GLYX-13, a NMDA receptor glycine-site functional partial agonist, induces antidepressant-like effects without ketamine-like side effects. *Neuropsychopharmacology* **2013,** *38* (5), 729.
231. Carrier, N.; Kabbaj, M., Sex differences in the antidepressant-like effects of ketamine. *Neuropharmacology* **2013,** *70*, 27-34.
232. Gigliucci, V.; O'Dowd, G.; Casey, S.; Egan, D.; Gibney, S.; Harkin, A., Ketamine elicits sustained antidepressant-like activity via a serotonin-dependent mechanism. *Psychopharmacology* **2013,** *228* (1), 157-166.
233. Koike, H.; Fukumoto, K.; Iijima, M.; Chaki, S., Role of BDNF/TrkB signaling in antidepressant-like effects of a group II metabotropic glutamate receptor antagonist in animal models of depression. *Behavioural brain research* **2013,** *238*, 48-52.
234. Koike, H.; Iijima, M.; Chaki, S., Effects of ketamine and LY341495 on the depressive-like behavior of repeated corticosterone-injected rats. *Pharmacology Biochemistry and Behavior* **2013,** *107*, 20-23.
235. Müller, H. K.; Wegener, G.; Liebenberg, N.; Zarate Jr, C. A.; Popoli, M.; Elfving, B., Ketamine regulates the presynaptic release machinery in the hippocampus. *Journal of psychiatric research* **2013,** *47* (7), 892-899.
236. Walker, A. K.; Budac, D. P.; Bisulco, S.; Lee, A. W.; Smith, R. A.; Beenders, B.; Kelley, K. W.; Dantzer, R., NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice. *Neuropsychopharmacology* **2013,** *38* (9), 1609.
237. Iijima, M.; Fukumoto, K.; Chaki, S., Acute and sustained effects of a metabotropic glutamate 5 receptor antagonist in the novelty-suppressed feeding test. *Behavioural brain research* **2012,** *235* (2), 287-292.
238. Koike, H.; Iijima, M.; Chaki, S., Involvement of the mammalian target of rapamycin signaling in the antidepressant-like effect of group II metabotropic glutamate receptor antagonists. *Neuropharmacology* **2011,** *61* (8), 1419-1423.
239. Liu, R.-J.; Fuchikami, M.; Dwyer, J. M.; Lepack, A. E.; Duman, R. S.; Aghajanian, G. K., GSK-3 inhibition potentiates the synaptogenic and antidepressant-like effects of subthreshold doses of ketamine. *Neuropsychopharmacology* **2013,** *38* (11), 2268.
240. Yang, C.; Hu, Y.-M.; Zhou, Z.-Q.; Zhang, G.-F.; Yang, J.-J., Acute administration of ketamine in rats increases hippocampal BDNF and mTOR levels during forced swimming test. *Upsala journal of medical sciences* **2013,** *118* (1), 3-8.

241. Yang, C.; Li, X.; Wang, N.; Xu, S.; Yang, J.; Zhou, Z., Tramadol reinforces antidepressant effects of ketamine with increased levels of brain-derived neurotrophic factor and tropomyosin-related kinase B in rat hippocampus. *Frontiers of medicine* **2012,** *6* (4), 411-415.
242. Wang, X.; Yang, Y.; Zhou, X.; Wu, J.; Li, J.; Jiang, X.; Qu, Q.; Ou, C.; Liu, L.; Zhou, S., Propofol pretreatment increases antidepressant-like effects induced by acute administration of ketamine in rats receiving forced swimming test. *Psychiatry Research* **2011,** *185* (1-2), 248-253.
243. Beurel, E.; Song, L.; Jope, R., Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. *Molecular psychiatry* **2011,** *16* (11), 1068.
244. Réus, G. Z.; Stringari, R. B.; Ribeiro, K. F.; Ferraro, A. K.; Vitto, M. F.; Cesconetto, P.; Souza, C. T.; Quevedo, J., Ketamine plus imipramine treatment induces antidepressant-like behavior and increases CREB and BDNF protein levels and PKA and PKC phosphorylation in rat brain. *Behavioural brain research* **2011,** *221* (1), 166-171.
245. Li, N.; Lee, B.; Liu, R.-J.; Banasr, M.; Dwyer, J. M.; Iwata, M.; Li, X.-Y.; Aghajanian, G.; Duman, R. S., mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* **2010,** *329* (5994), 959-964.
246. Ghasemi, M.; Raza, M.; Dehpour, A., NMDA receptor antagonists augment antidepressant-like effects of lithium in the mouse forced swimming test. *Journal of Psychopharmacology* **2010,** *24* (4), 585-594.
247. Cruz, S. L.; Soberanes-Chávez, P.; Páez-Martinez, N.; López-Rubalcava, C., Toluene has antidepressant-like actions in two animal models used for the screening of antidepressant drugs. *Psychopharmacology* **2009,** *204* (2), 279-286.
248. Engin, E.; Treit, D.; Dickson, C., Anxiolytic-and antidepressant-like properties of ketamine in behavioral and neurophysiological animal models. *Neuroscience* **2009,** *161* (2), 359-369.
249. Rezin, G. T.; Gonçalves, C. L.; Daufenbach, J. F.; Fraga, D. B.; Santos, P. M.; Ferreira, G. K.; Hermani, F. V.; Comim, C. M.; Quevedo, J.; Streck, E. L., Acute administration of ketamine reverses the inhibition of mitochondrial respiratory chain induced by chronic mild stress. *Brain research bulletin* **2009,** *79* (6), 418-421.
250. Garcia, L. S.; Comim, C. M.; Valvassori, S. S.; Réus, G. Z.; Barbosa, L. M.; Andreazza, A. C.; Stertz, L.; Fries, G. R.; Gavioli, E. C.; Kapczinski, F., Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Progress in neuro-psychopharmacology and biological psychiatry* **2008,** *32* (1), 140-144.
251. Hayase, T.; Yamamoto, Y.; Yamamoto, K., Behavioral effects of ketamine and toxic interactions with psychostimulants. *BMC neuroscience* **2006,** *7* (1), 25.
252. Rosa, A. O.; Lin, J.; Calixto, J. B.; Santos, A. R. S.; Rodrigues, A. L. S., Involvement of NMDA receptors and L-arginine-nitric oxide pathway in the antidepressant-like effects of zinc in mice. *Behavioural brain research* **2003,** *144* (1-2), 87-93.
253. Mantovani, M.; Pértile, R.; Calixto, J. B.; Santos, A. R.; Rodrigues, A. L. S., Melatonin exerts an antidepressant-like effect in the tail suspension test in mice: evidence for involvement of N-methyl-D-aspartate receptors and the L-arginine-nitric oxide pathway. *Neuroscience letters* **2003,** *343* (1), 1-4.
254. Denayer, T.; Stöhr, T.; Roy, M. V., Animal models in translational medicine: Validation and prediction. *European Journal of Molecular & Clinical Medicine* **2014,** *2* (1), 5.
255. Demin, K.; Meshalkina, D.; Lakstygal, A.; Kalueff, A., Developing translational biological psychiatry: learning from history to build the future. **2017**.
256. Aragona, M., The role of comorbidity in the crisis of the current psychiatric classification system. *Philosophy, Psychiatry, & Psychology* **2009,** *16* (1), 1-11.
257. Aragona, M., The concept of mental disorder and the DSM-V. **2009**.
258. Kato, T., A renovation of psychiatry is needed. *World Psychiatry* **2011,** *10* (3), 198-199.
259. Gottesman, I. I.; Shields, J., Schizophrenia and genetics. A twin study vantage point. In *ACAD. PRESS, NEW YORK, NY*, 1972.
260. Gottesman, I. I.; Shields, J., Genetic theorizing and schizophrenia. *The British Journal of Psychiatry* **1973,** *122* (566), 15-30.

261. Gottesman, II; Gould, T. D., The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* **2003,** *160* (4), 636-45.
262. Kalueff, A. V.; Ren-Patterson, R. F.; LaPorte, J. L.; Murphy, D. L., Domain interplay concept in animal models of neuropsychiatric disorders: a new strategy for high-throughput neurophenotyping research. *Behav Brain Res* **2008,** *188* (2), 243-9.
263. Kalueff, A. V.; Stewart, A. M., Modeling neuropsychiatric spectra to empower translational biological psychiatry. *Behav Brain Res* **2015,** *276*, 1-7.
264. Kas, M. J.; Fernandes, C.; Schalkwyk, L. C.; Collier, D. A., Genetics of behavioural domains across the neuropsychiatric spectrum; of mice and men. *Mol Psychiatry* **2007,** *12* (4), 324-30.
265. Crabbe, J. C.; Morris, R. G., Festina lente: late-night thoughts on high-throughput screening of mouse behavior. *Nature neuroscience* **2004,** *7* (11), 1175.
266. Godinho, S. I.; Nolan, P. M., The role of mutagenesis in defining genes in behaviour. *European journal of human genetics* **2006,** *14* (6), 651.
267. Tecott, L. H.; Nestler, E. J., Neurobehavioral assessment in the information age. *Nature neuroscience* **2004,** *7* (5), 462.
268. Kalueff, A. V.; LaPorte, J. L.; Murphy, D. L.; Sufka, K., Hybridizing behavioral models: a possible solution to some problems in neurophenotyping research? *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **2008,** *32* (5), 1172-1178.
269. Kalueff, A. V.; Aldridge, J. W.; LaPorte, J. L.; Murphy, D. L.; Tuohimaa, P., Analyzing grooming microstructure in neurobehavioral experiments. *Nature protocols* **2007,** *2* (10), 2538.
270. Leussis, M. P.; Bolivar, V. J., Habituation in rodents: a review of behavior, neurobiology, and genetics. *Neuroscience & Biobehavioral Reviews* **2006,** *30* (7), 1045-1064.
271. Uhlhaas, P. J.; Singer, W., Neuronal dynamics and neuropsychiatric disorders: toward a translational paradigm for dysfunctional large-scale networks. *Neuron* **2012,** *75* (6), 963-980.
272. Marsh, R.; Gerber, A. J.; Peterson, B. S., Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. *Journal of the American Academy of Child & Adolescent Psychiatry* **2008,** *47* (11), 1233-1251.
273. Kudryavtseva, N. N.; Bakshtanovskaya, I. V.; Koryakina, L. A., Social model of depression in mice of C57BL/6J strain. *Pharmacol Biochem Behav* **1991,** *38* (2), 315-20.
274. Kudryavtseva, N., Peculiarities in forming agonistic behavior in mice using a sensory contact model. *Review Novosibirsk: Institute of Cytology and Genetics SD RAS* **1987**.
275. Kudryavtseva, N.; Bakshtanovskaya, I., Development of depression like states in C57BL/6J submissive male mice (prepn'nt). *Institute of Cytology and Genetics: Novosibirsk [in Russian]* **1988**.
276. Kudryavtseva, N.; Bakshtanovskaya, I.; Koryakina, L., Social model of depression in mice of C57BL/6J strain. *Pharmacology Biochemistry and Behavior* **1991,** *38* (2), 315-320.
277. Avgustinovich, D.; Alekseenko, O.; Bakshtanovskaia, I.; Koriakina, L.; Lipina, T.; Tenditnik, M.; Kovalenko, I.; Kudriavtseva, N., Dynamic changes of brain serotonergic and dopaminergic activities during development of anxious depression: experimental study. *Uspekhi fiziologicheskikh nauk* **2004,** *35* (4), 19-40.
278. Galyamina, A.; Kovalenko, I.; Smagin, D.; Kudryavtseva, N., Interaction of Depression and Anxiety in the Development of Mixed Anxiety/Depression Disorder. Experimental Studies of the Mechanisms of Comorbidity. *Neuroscience and Behavioral Physiology* **2017,** *47* (6), 699-713.
279. Kola, I.; Landis, J., Can the pharmaceutical industry reduce attrition rates? *Nature reviews Drug discovery* **2004,** *3* (8), 711.
280. Pangalos, M. N.; Schechter, L. E.; Hurko, O., Drug development for CNS disorders: strategies for balancing risk and reducing attrition. *Nature Reviews Drug Discovery* **2007,** *6* (7), 521.
281. Choi, D. W.; Armitage, R.; Brady, L. S.; Coetzee, T.; Fisher, W.; Hyman, S.; Pande, A.; Paul, S.; Potter, W.; Roin, B., Medicines for the mind: policy-based “Pull” incentives for creating breakthrough CNS drugs. *Neuron* **2014,** *84* (3), 554-563.

282. Maniam, J.; Morris, M. J., Long-term postpartum anxiety and depression-like behavior in mother rats subjected to maternal separation are ameliorated by palatable high fat diet. *Behav Brain Res* **2010,** *208* (1), 72-9.
283. Pryce, C. R.; Ruedi-Bettschen, D.; Dettling, A. C.; Weston, A.; Russig, H.; Ferger, B.; Feldon, J., Long-term effects of early-life environmental manipulations in rodents and primates: Potential animal models in depression research. *Neurosci Biobehav Rev* **2005,** *29* (4-5), 649-74.
284. Ivy, A. S.; Rex, C. S.; Chen, Y.; Dube, C.; Maras, P. M.; Grigoriadis, D. E.; Gall, C. M.; Lynch, G.; Baram, T. Z., Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *J Neurosci* **2010,** *30* (39), 13005-15.
285. Rice, C. J.; Sandman, C. A.; Lenjavi, M. R.; Baram, T. Z., A novel mouse model for acute and long-lasting consequences of early life stress. *Endocrinology* **2008,** *149* (10), 4892-900.
286. Sudo, N.; Chida, Y.; Aiba, Y.; Sonoda, J.; Oyama, N.; Yu, X. N.; Kubo, C.; Koga, Y., Postnatal microbial colonization programs the hypothalamic–pituitary–adrenal system for stress response in mice. *The Journal of physiology* **2004,** *558* (1), 263-275.
287. Leith, N. J.; Barrett, R. J., Effects of chronic amphetamine or reserpine on self-stimulation responding: Animal model of depression? *Psychopharmacology* **1980,** *72* (1), 9-15.
288. Sethy, V. H.; Hodges Jr, D. H., Antidepressant activity of alprazolam in a reserpine-induced model of depression. *Drug development research* **1985,** *5* (2), 179-184.
289. Piato, A. L.; Rosemberg, D. B.; Capiotti, K. M.; Siebel, A. M.; Herrmann, A. P.; Ghisleni, G.; Vianna, M. R.; Bogo, M. R.; Lara, D. R.; Bonan, C. D., Acute restraint stress in zebrafish: behavioral parameters and purinergic signaling. *Neurochem Res* **2011,** *36* (10), 1876-86.
290. Piato, A. L.; Capiotti, K. M.; Tamborski, A. R.; Oses, J. P.; Barcellos, L. J.; Bogo, M. R.; Lara, D. R.; Vianna, M. R.; Bonan, C. D., Unpredictable chronic stress model in zebrafish (Danio rerio): behavioral and physiological responses. *Prog Neuropsychopharmacol Biol Psychiatry* **2011,** *35* (2), 561-7.
291. Saszik, S. M.; Smith, C. M., The impact of stress on social behavior in adult zebrafish (Danio rerio). *Behavioural pharmacology* **2018,** *29* (1), 53-59.
292. Kato, T.; Kubota, M.; Kasahara, T., Animal models of bipolar disorder. *Neurosci Biobehav Rev* **2007,** *31* (6), 832-42.
293. Kyzar, E.; Stewart, A. M.; Landsman, S.; Collins, C.; Gebhardt, M.; Robinson, K.; Kalueff, A. V., Behavioral effects of bidirectional modulators of brain monoamines reserpine and d-amphetamine in zebrafish. *Brain Res* **2013,** *1527*, 108-16.
294. Wang, Y.; Liu, W.; Yang, J.; Wang, F.; Sima, Y.; Zhong, Z. M.; Wang, H.; Hu, L. F.; Liu, C. F., Parkinson's disease-like motor and non-motor symptoms in rotenone-treated zebrafish. *Neurotoxicology* **2017,** *58*, 103-109.
295. Li, X.; Liu, X.; Li, T.; Li, X.; Feng, D.; Kuang, X.; Xu, J.; Zhao, X.; Sun, M.; Chen, D., SiO 2 nanoparticles cause depression and anxiety-like behavior in adult zebrafish. *RSC Advances* **2017,** *7* (5), 2953-2963.
296. Ziv, L.; Muto, A.; Schoonheim, P. J.; Meijsing, S. H.; Strasser, D.; Ingraham, H. A.; Schaaf, M. J.; Yamamoto, K. R.; Baier, H., An affective disorder in zebrafish with mutation of the glucocorticoid receptor. *Mol Psychiatry* **2013,** *18* (6), 681-91.
297. Griffiths, B. B.; Schoonheim, P. J.; Ziv, L.; Voelker, L.; Baier, H.; Gahtan, E., A zebrafish model of glucocorticoid resistance shows serotonergic modulation of the stress response. *Front Behav Neurosci* **2012,** *6*, 68.