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Animal Models of Suicide Trait-Related Behaviors

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Abstract

Although antidepressants are at least moderately effective in treating major depressive disorder (MDD), concerns have arisen that selective serotonin reuptake inhibitors (SSRIs) are associated with suicidal thinking and behavior, especially in children, adolescents, and young adults. Virtually no experimental research in model systems has considered the mechanisms by which SSRIs may be associated with this potential side effect in *some susceptible individuals*. Suicide is a complex behavior that is, at best, complicated to study in humans and impossible to fully reproduce in an animal model. However, by investigating traits that show strong cross-species parallels as well as associations with suicide in humans, animal models may elucidate the mechanisms by which SSRIs are associated with suicidal thinking and behavior in the young. Traits linked with suicide in humans that can be successfully modeled in rodents include aggression, impulsivity, irritability, and hopelessness/helplessness. Differences in animal response to particular paradigms and to SSRIs across the lifespan are also discussed. Modeling these relevant traits in animals can help clarify the impact of SSRIs on these traits, suggesting avenues for reducing suicide risk in this vulnerable population.

Keywords

SSRI; suicide; animal model; aggression; impulsivity; helplessness; irritability

Introduction

In 2005, suicide was the eleventh leading cause of death in the United States [1]. For individuals aged 5–14, however, suicide was the fourth, and for those aged 15–24, it was the third leading cause of death. Suicide in young people is a global concern, and youth suicide prevention is a major priority in most countries [2].

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The risk of suicide during antidepressant drug treatment—specifically during treatment with selective serotonin reuptake inhibitors (SSRIs)—has been debated for more than 40 years. Although some studies have supported this association [3], others have noted methodological limitations that preclude firm conclusions [4,5]. Considerable controversy surrounds the specific relationship between antidepressants and suicide in the young. Major depressive disorder (MDD) is the most frequent diagnosis among youths committing suicide [6], and antidepressant medications are at least moderately effective in treating MDD in the young [7]. However, concerns have arisen that antidepressants in general, and SSRIs in particular, may actually increase risk for suicidal thoughts and behavior in this population [5]. Based on data supporting this concern, in October 2004 the U.S. Food and Drug Administration (FDA) ordered pharmaceutical companies to add a black box warning—the FDA's most serious drug warning label—regarding the possible link between antidepressant treatment and suicide in children and adolescents [8]. This warning was expanded in May 2007 to encompass increased risk of suicidal symptoms in young adults 18 to 24 years of age, based on new data indicating that this group was also at risk [9]. The new warning also stated that there was no evidence of increased risk for adults older than age 24.

Although the FDA panel endorsed the risk of antidepressant-related suicidality, the precise nature of this relationship is poorly understood due to two limitations. First, researchers conducting clinical trials of antidepressant efficacy collected few details for some patients regarding the nature of the particular events involving suicidal thoughts or behavior, which may have compromised the degree of accuracy in classifying each event as a "true" instance of suicidal behavior. Moreover, no instances of completed suicide were observed in any trial, nor did the available data precisely elucidate the specific behaviors altered by antidepressants. While suicidal thoughts and behaviors represent reasonable predictors of risk for completed suicide, the overwhelming majority of individuals exhibiting these features will not commit suicide. Second, considerable heterogeneity was present across randomized control trials in terms of the antidepressant studied, patient characteristics, number of sites, and data collection procedures. Furthermore, certain studies found no significant correlation between SSRI treatment and suicide in children and/or adolescents [10]. Notably, a US study of children and adolescents aged 10 to 19 years found a significant inverse relationship for changes in regional rates of antidepressant medication treatment and changes in regional suicide rates [11]. For each one percent increase in the use of SSRIs among adolescents, there was a decrease of 0.23 suicides per 100,000 adolescents per year. This finding is consistent with other studies showing a decline in US youth suicide rates after the introduction of SSRIs [12].

The evidence reviewed above highlights the need to identify the mechanisms by which SSRIs may be associated with the potential side effect of suicide in *some susceptible individuals* [3], so that life-saving medications are not withheld from those not at risk (see Box 1 for further discussion of SSRIs and the role of serotonin in depressive disorders). The potential use of animal models to elucidate this issue is the focus of this paper.

Box 1

SSRIs and Depressive Symptoms

Selective serotonin reuptake inhibitors (SSRIs) encompass a large class of antidepressant drugs available to treat depression. All SSRIs, through different mechanisms, increase serotonin levels in the synapse by preventing presynaptic reuptake of this neurotransmitter. Although acute treatment with SSRIs can elicit a rapid change in serotonin levels, this does not correlate well with changes in affect; typically, mood improves after chronic treatment (14–30 days). In addition, SSRIs are associated with a remission rate of 30–40%, limiting their long-term efficacy in the general population. Thus, the acute changes in monoamine levels produced by SSRIs do not appear to be intrinsically beneficial, but may instead

activate intracellular cascades that lead to prolonged changes in neuroplasticity [72]. Furthermore, serotonergic dysfunction is strongly implicated in the development of unipolar depression, though it is likely that altered monoamine levels alone cannot explain this disorder. The serotonin network itself originates in the brain stem, but projects to most brain regions, including those implicated in mood disorders (e.g. the limbic system and cortex).

The usefulness of SSRIs in treating depression has long suggested that serotonin is critical to the etiology or pathophysiology of depression, and many studies support the idea that disrupted production or release of serotonin and other neurotransmitters contributes to the neurobiological basis of this disorder. Evidence from challenge, genetic, and antidepressant studies, as well as studies of serotonin metabolism in cerebrospinal fluid (CSF) and investigations of serotonin receptors, all support the involvement of the serotonergic system in the pathophysiology of depression (summarized in [73]). For instance, CSF studies have noted reduced CSF 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, in both suicidal and impulsive/aggressive patients, regardless of whether they were diagnosed with MDD or bipolar disorder; furthermore, depressed patients were found to have significantly lower maximal velocity of serotonin uptake in the CSF compared with matched controls. In challenge studies, a tryptophan depletion diet induced a rapid depressive relapse in SSRI-treated patients; this is particularly notable because serotonin is synthesized from tryptophan. In addition, in healthy subjects, intravenous infusion of tryptophan increased prolactin plasma levels, although this release was blunted in depressed patients. Other studies have revealed that individuals with MDD have a blunted physiological response to serotonin receptor (5-HT1A)-agonists in vivo and abnormal 5-HT1A receptor binding postmortem. Similarly, recent positron emission tomography (PET) studies have yielded in vivo evidence of reduced pre-and postsynaptic 5-HT1A receptor binding in individuals with MDD. Several studies also reported an increased number of postsynaptic 5HT2 receptors in the brains of depressed patients as well as suicide victims.

Antidepressant studies have also noted the antidepressant efficacy of agents that increase intrasynptic serotonin. Relatedly, chronic antidepressants generally reduce serotonin turnover in patients, even agents whose primary biochemical target is not the serotonergic system. Chronic treatment with SSRIs reduce cell body 5-HT1A density, thereby increasing serotonergic neuron firing; indeed, antidepressants generally decrease 5-HT2 density in rat prefrontal cortex. Genetic studies have also noted that the 5-HTTLPR short variant is associated with poor response to fluoxetine in individuals with MDD, that the 5-HT5A gene allelic association was found with the 19G/C polymorphism and MDD, and that an increase in the 5-HT2C receptor gene (Cys 23 Ser) allele was associated with MDD. Thus, data from a variety of studies suggest that abnormalities of the serotonergic system are present in MDD.

Recent investigations have examined the molecular basis of chronic SSRI treatment, providing new insight into their mechanism of action and helping to better understand the role of serotonin in depression. Animal studies have revealed that chronic antidepressant treatment alters critical regulators of neuroplastic function, including the mitogen-activated protein kinase (MAPK) pathway, brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and cyclic AMP response binding element (CREB) (reviewed in [72]). Post-mortem findings also support SSRI-mediated increases in CREB activity, which appears to be less abundantly expressed in the temporal cortex of severely depressed individuals [74]. Work is currently underway to further examine how SSRIs alter synaptic and network function via intracellular cascades, and how these changes relate to monoamine synthesis, release, and reuptake at the synapse.

Animal models are essential for translational research. Although limitations in animal models have been duly noted [13], many fundamental physiological and behavioral responses have been evolutionarily conserved between species, and these responses can elucidate phenotypes relevant to human emotional behaviors [14]. An animal model is defined as any experimental paradigm developed in an animal for the express purpose of studying a human condition; however no perfect animal model exists for any aspect of any psychiatric disorder.

With regards to suicide, the most obvious limitation of the animal model strategy is the vastly different behavior of humans compared to any other animal. Suicide is a complex behavior, and there are no existing animal models for suicide per se, or for self-aggression, although some evidence exists of deliberate self-endangering behavior among animal species [15]. In the context of this article, it is important to note that while it is obviously not possible to develop an animal model of suicide that has face validity for that behavior, specific traits associated with suicide in humans can be successfully modeled in animals. Specifically, the involvement of personality traits in susceptibility to suicidality has been the subject of research since the 1950s, and numerous studies have identified personality traits that are risk factors for suicidal behavior [16,17]. Studying the results from various paradigms that model these traits in animals can provide a starting point for examining the mechanisms through which SSRIs may act to increase or decrease suicide risk.

The current paper will focus on modeling four major risk factors associated with suicidal behavior in humans: aggression, impulsivity, irritability, and hopelessness/helplessness (Table 1 and Figures 1–4 summarize the most often used and best-known of these paradigms). These four traits are known to correlate with suicidal ideation, suicide attempts, and suicide completion, and all can be successfully modeled and manipulated in animals [16]. In addition, antidepressants, particularly SSRIs, can reliably induce these behaviors in animal models [3]. Thus, animal models may prove very useful in the investigation of these effects in patients who are prescribed SSRIs. In the context of this paper, it is important to note that most of the relevant animal studies conducted to date have focused on adult rodents; however, any animal model attempting to thoroughly assess the impact of SSRIs on suicidality in the young would need to investigate this paradigm in pre-pubertal and juvenile rodents, in order to differentiate these behavioral differences across the life span (*vide infra*).

Aggression

Multiple epidemiologic, clinical, retrospective, prospective, and family studies have identified a strong link between aggression and suicide [18]. Brent and colleagues found that a lifetime history of aggression differentiated adolescent suicide victims from matched controls, even after controlling for differences in psychopathology between suicides and controls [19]; these results are also consistent with those obtained by Shaffer and colleagues [6]. Renaud and colleagues found that high levels of aggression were associated with the risk of suicide in children and adolescents [20]. Studies of adolescent inpatients suggest that youth with a history of frequent violent behavior more frequently have a history of suicide attempts than non-violent inpatients [18]. Moreover, the association between aggression and suicide attempts in community and inpatient samples persists when mood and disruptive behavior problems are controlled [21]. Notably, the FDA analysis demonstrated that antidepressant treatment was associated with symptoms of treatment-emergent hostility or agitation [22].

Laboratory research has produced detailed descriptions of aggression and defense patterns in rats, mice, and hamsters, showing strong similarities, but also some differences, across species [23]. Furthermore, research with a focus on the stimulus antecedents of aggression, its response characteristics, and its outcomes, suggests a number of detailed correspondences between offensive aggression in laboratory rodents and human aggression (e.g., resource competition) [24].

Many tests can be used to model aggression (see [25] for a thorough review of this topic), but the Resident Intruder paradigm is the most frequently used (See Table 1,Figure 1). Notably, the ability to reduce aggressive behavior in resident rodents in this paradigm is an ability shared by acute treatment with all the pharmacologically disparate antidepressant compounds tested, including SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and atypical antidepressants such as mianserin and iprindole. In contrast, chronic treatment with these disparate compounds increases aggressive behavior in rats [26]. Interestingly, and in contrast to the rat studies, the aggressive behavior of male mice in the resident-intruder studies is particularly sensitive to anxiolytic, rather than antidepressant, drug activity [27]. This species difference in response to antidepressant and anxiolytic drugs is most likely due to the functional differences in aggressive behavior between rats and mice; mice will violently defend their territory, while rats live in social colonies where excessively violent behavior is detrimental to the social group [27].

One avenue of research that merits further study is the role of the serotonergic system in mediating the behavioral effects of SSRIs on aggression. Several studies found that, in young boys, social circumstances that are conducive to the development of aggressive behaviors are positively correlated with a marker of central serotonergic activity [28]. In addition, mice with selected genetic targeting of the serotonergic system exhibit severe to mild behavioral alterations. For instance, Pet1 knockout (KO) mice showed increased aggression [29]; Pet-1 E26 Transformation Specific (ETS) factor is a precise marker of developing and adult serotonergic neurons and is expressed shortly before serotonin appears in the hindbrain. In addition, aggression was found to be elevated in MAO-A inhibited mice only after acute pharmacologic challenge, suggesting prenatal sensitization [30].

Impulsivity

The behavioral expressions of impulsivity include disturbed inhibition of behavior, lack of reflection regarding the consequences of one's behavior, and inability to postpone reward (delay aversion) [31]. Although the findings are not consistent, many studies support the role of impulsivity in suicidal behavior. Evidence also suggests that suicide completers, and most notably younger ones, have higher levels of impulsivity than controls [32]. Adolescents use more non-specific medications (e.g., non-narcotic analgesics) and cut themselves more frequently than adults when attempting suicide, which may reflect increased impulsivity in this age group, especially because the influence of age is independent from the influence of gender or diagnosis [33]. Conwell and colleagues found that older age was significantly associated with more predetermined and planned self-destructive acts, less violent methods, and fewer warnings of suicidal intent [34]. Other reports also support the notion that younger suicides are more likely to be the result of an impulsive act. One study found that, of those who attempted suicide, 75% took less than one hour to make the decision; 25% took less than five minutes, 24% took less than 10 minutes, and only seven percent thought for more than 24 hours [35]. Interestingly, a series of studies of suicide completers found that high levels of impulsivity correlated strongly and significantly with high levels of aggressive behavior or hostility; the authors also found an important age effect [32].

During the course of SSRI treatment, some children may experience an "activation syndrome" characterized by signs of hyperarousal and impulsivity [36]. In addition, various forms of aggressive behavior have been found to be significantly associated with increased sensation-seeking and impulsivity [37]. Therefore, some researchers have suggested that the treatment of impulsive aggression or the provision of violence prevention interventions might reduce suicide risk [38]. However, additional work to explore the mechanism(s) by which SSRIs may

enhance impulsivity and/or aggression during specific developmental phases is clearly necessary.

Various preclinical models have greatly contributed to our understanding of the neural correlates of impulsivity in rodents [31]. Different aspects of impulsivity can be studied with operant-behavior paradigms in laboratory settings (See Table 1,Figure 2) that typically assess impulsivity based on choices that the animal makes. Though limited, these models of impulsivity are sensitive to both pharmacological manipulations and selective brain lesions in animals [39].

Irritability

Another major risk factor for suicidality is irritability [17], defined as "…a feeling state characterized by reduced control over temper which usually results in irascible verbal or behavioural outbursts, although the mood may be present without observed manifestation" (p. 128) [40].

Several studies found that irritability is strongly associated with suicidal ideation and suicide attempts [41]. Akiskal & Benazzi (2006) found that patients with suicidal ideation had 1.32 greater odds of also having irritability than those without suicidal ideation. In addition, irritable adolescent males appear to be more likely to contemplate suicidal behavior than those who do not display irritability [41]. These results support the FDA's suggested correlates of suicidality, which state that parents of depressed children receiving antidepressants should watch for new or worse levels of irritability in their children [42]. In addition, one of the most common symptoms reported by children with a range of psychiatric conditions is irritability [43]. Episodic irritability shows a linear variation with age, whereas chronic irritability shows a quadratic variation with a peak in mid-adolescence [44]. Several studies have found a specific association between chronic irritability and MDD, where chronic, subsyndromal symptoms such as irritability predict the later onset of MDD [43,45]. Notably, antidepressants have been shown to increase irritability in several open clinical case series [46].

Irritability has been studied in rodents for many years. It has been described when the animal becomes wild and/or restless in response to a tactile or auditory stimulus [47], and it has more recently been defined as an extreme reaction to relatively minute stimuli [48]. However, as opposed to aggression and impulsivity, irritability, at least in humans, is not purely "behaviorally" defined but involves some level of subjective state changes, even in children [49]; therefore the modeling of irritability in rodents is particularly complicated.

Several paradigms are used to measure irritability in laboratory animals (see Table 1, Figure 3), and a variety of drugs can induce irritability in rodents including para-chlorophenylalanine (PCPA) [50], trimethyltin [51], midazole [51], etc. However, irritable behavior in rodents appears to occur most robustly and frequently during periods of psychoactive drug withdrawal, especially for opiate drugs [52,53]. Opiate withdrawal is relatively simple to induce and therefore can be easily used as part of a test battery. Methods also exist to evaluate withdrawal without drugs, thereby establishing an environmental/behavioral avenue to induce irritability [52].

Hopelessness/Helplessness

One of the most prominent correlates of suicidal ideation is hopelessness, although its importance may vary across age groups [17]. Hopelessness has been defined in the DSM-IV [54] as a pervasive pessimism about the future. It has been found to significantly predict suicidal ideation [55]. In addition, studies have shown that symptoms of low self-esteem and hopelessness in teenage boys lead to thoughts of self-harm [56]. Most studies have also found

that hopelessness is an important risk factor for suicide completion [17]. In a longitudinal study of patients with affective disorders, hopelessness differentiated between attempts and completions [57]. In addition, levels of hopelessness were greater in completers in several long-term prospective studies involving hospitalized suicidal ideators and psychiatric outpatients [58].

As with irritability, hopelessness involves the assessment of some level of subjective state changes [56], which make modeling hopelessness in rodents very complicated. In animal models, the most often used proxy for assessing hopelessness is the learned helplessness paradigm [59] (see Table 1,Figure 4), which has been conducted successfully in several species, including rats and mice [60]. The learned helplessness paradigm is used in preclinical pharmacological studies to assess the antidepressant effect of new compounds. TCAs, MAOIs, and atypical antidepressants, including SSRIs, all prevent and reverse learned helplessness in animals [61]. One study showed that female mice treated neonatally with an SSRI exhibited increased helplessness that was reversed by chronic antidepressant treatment [62].

Age as a variable in the research of behaviors related to suicide traits—One issue of particular relevance to this discussion is that of age. As noted in the Introduction, the FDA black box warning regarding the link between suicide and SSRIs is age-dependent, affecting children and adolescents. Although some studies exist regarding age-related changes in rodents for the behaviors described above, very few studies discuss the effects of different medications (especially antidepressants) on these behaviors as a function of age. This is a crucial point that needs careful investigation.

The concept of behavior is in itself complicated by the fact that the intrinsic arousability of underlying brain systems may change in many ways as organisms age [63]. For instance, behaviors related to fear, anger, and separation distress emerge at early developmental stages, allowing young animals to cope with emergency situations that could compromise their survival. As organisms age however, they develop more complex and subtle feelings and behaviors [63]. Some of the specific behaviors discussed above do indeed show developmental patterns that imply specific changes in brain systems as the organism ages. Puberty, for instance, is marked by a transition from play fighting to adult aggression in most mammalian species [64], although the patterns of development of this transmission may vary between species [65]. Indeed, aggression behaviors undergo significant transitions during different phases of development in the life span of rodents [65]. Other research has shown that adult rats exhibit different levels of impulsivity and responsiveness to drug treatment compared to juvenile animals of the same strain [66].

Although the data on how developmental behavioral patterns correlate with changes in brain systems during the life span are sparse, the data that are available suggest that these differences are not negligible. For instance, studies found that anatomical changes in myelination of the prefrontal cortex play an important role in affect control and responsiveness to stressors [67], and that adolescent males are more vulnerable to the loss of control that leads to hopelessness [67]. In addition, basal dopamine levels in rodents are age-dependent [68]. Thus, a good animal model for these purposes should determine changes in those behaviors in response to different antidepressants in at least three different age groups (“childhood”, “adolescent”, and “adult”); notably, in rodents “childhood” loosely refers to post-natal day (PND) 21-35, “adolescent” refers to PND 36-59, and “adult” refers to PND 60-90 [63]. Information gleaned from such work, especially from changes seen in young animals, will help researchers assess the extent to which the FDA black box decision is justified. Presently, available data on the development of the specific traits described above aggression, impulsivity, irritability, and hopelessness/helplessness are very limited, as are data on the influence of pharmacological manipulations on these traits across the life span of rodents. However, different characteristics of impulsivity

can be observed over the life span of rodents [69], and it is known that both juvenile and adolescent rats can display helplessness in the learned helplessness paradigm [70].

Conclusions and Summary

MDD is the second most common psychiatric disorder in the United States [71], and although the need to develop new antidepressant treatments persists, considerable data show that the common antidepressants are effective in treating MDD for a large proportion of afflicted patients. Concerns that SSRIs were potentially associated with suicidal thinking and behavior in children, adolescents, and young adults led the FDA to issue a black box warning for those medications [4,8]. A recent study found that the black box warning led to a decrease in SSRI prescriptions in the young, with a concomitant increase in suicides in this population [4]. Thus, there is clearly a need to identify the mechanisms by which SSRIs may be associated with this potential side effect in *some susceptible individuals*, so that life-saving medications are not withheld from those not at risk.

A promising direction for identifying the mechanisms by which SSRIs may be associated with suicide, especially in the young, is the use of animal models. Animal models are widely used in translational medical research, but to date no animal models of suicide have been developed. These are urgently needed to determine the precise effects of SSRIs on suicidal ideation and suicide attempts, and may prove useful in revealing the true risks of antidepressant use in the young. Although the development of an animal model for suicide *per se* is challenging and unlikely, several main risk factors for suicidal behavior can be modeled and manipulated easily in animals, including aggression, impulsivity, irritability, and helplessness behavior. These paradigms are useful tools for helping to identify and explore the mechanisms by which SSRIs may be associated with suicide. Future studies can help us understand the underlying mechanisms of antidepressants on these behaviors and on suicide risk and, ultimately, help determine the course of treatment for the millions of young people diagnosed with this devastating disorder.

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References

1. Hamilton BE, et al. Annual summary of vital statistics: 2005. Pediatrics 2007;119:345–360. [PubMed: 17272625]
2. Pelkonen M, Marttunen M. Child and adolescent suicide: epidemiology, risk factors, and approaches to prevention. Paediatr Drugs 2003;5:243–265. [PubMed: 12662120]
3. Goodman WK, et al. Risk of adverse behavioral effects with pediatric use of antidepressants. Psychopharmacology (Berl) 2007;191:87–96. [PubMed: 17180618]
4. Gibbons RD, et al. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. Am J Psychiatry 2007;164:1044–1049. [PubMed: 17606656]
5. Hammad TA, et al. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332–339. [PubMed: 16520440]
6. Shaffer D, et al. Psychiatric diagnosis in child and adolescent suicide. Arch Gen Psychiatry 1996;53:339–348. [PubMed: 8634012]
7. Bridge JA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 2007;297:1683–1696. [PubMed: 17440145]
8. Hamaad, TA. Washington, DC: Food and Drug Administration; Aug 16. 2004 Review and evaluation of clinical data.

9. Friedman RA, Leon AC. Expanding the black box - depression, antidepressants, and the risk of suicide. N Engl J Med 2007;356:2343–2346. [PubMed: 17485726]
10. Leon AC, et al. Paroxetine, other antidepressants, and youth suicide in New York City: 1993 through 1998. J Clin Psychiatry 2004;65:915–918. [PubMed: 15291679]
11. Olfson M, et al. Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 2003;60:978–982. [PubMed: 14557142]
12. Hall WD, et al. Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. BMJ 2003;326:1008. [PubMed: 12742921]
13. Crawley, JN. What's wrong with my mouse? Behavioral phenotyping of transgenic and knockout mice. New York: Wiley-Liss; 2000.
14. Cryan JF, Mombereau C. In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. Mol Psychiatry 2004;9:326–357. [PubMed: 14743184]
15. Crawley JN, et al. Animal models of self-destructive behavior and suicide. Psychiatr Clin North Am 1985;8:299–310. [PubMed: 2410895]
16. Mann JJ, et al. The neurobiology and genetics of suicide and attempted suicide: a focus on the serotonergic system. Neuropsychopharmacology 2001;24:467–477. [PubMed: 11282247]
17. Brezo J, et al. Personality traits as correlates of suicide attempts and suicidal ideation in young adults. Psychol Med 2006;36:191–202. [PubMed: 16332283]
18. Grosz DE, et al. Correlates of violence risk in hospitalized adolescents. Compr Psychiatry 1994;35:296–300. [PubMed: 7956186]
19. Brent DA, et al. Familial risk factors for adolescent suicide: a case-control study. Acta Psychiatr Scand 1994;89:52–58. [PubMed: 8140907]
20. Renaud J, et al. Current psychiatric morbidity, aggression/impulsivity, and personality dimensions in child and adolescent suicide: a case-control study. J Affect Disord 2008;105:221–228. [PubMed: 17568682]
21. Haavisto A, et al. Suicidal ideation and suicide attempts among child and adolescent psychiatric inpatients in Finland. J Affect Disord 2003;76:211–221. [PubMed: 12943951]
22. FDA. Revisions to Medication Guide. 2007. http://www.fda.gov/cder/drug/antidepressants/antidepressants_MG_2007.pdf
23. Blanchard RJ, et al. Problems in the study of rodent aggression. Horm Behav 2003;44:161–170. [PubMed: 14609538]
24. Blanchard DC, Blanchard RJ. What can animal aggression research tell us about human aggression? Horm Behav 2003;44:171–177. [PubMed: 14609539]
25. Miczek KA, et al. Aggressive behavioral phenotypes in mice. Behav Brain Res 2001;125:167–181. [PubMed: 11682108]
26. Mitchell PJ. Antidepressant treatment and rodent aggressive behaviour. Eur J Pharmacol 2005;526:147–162. [PubMed: 16289453]
27. Lumley MA. Alexithymia and negative emotional conditions. J Psychosom Res 2000;49:51–54. [PubMed: 11203601]
28. Pine DS, et al. Neuroendocrine response to fenfluramine challenge in boys. Associations with aggressive behavior and adverse rearing. Arch Gen Psychiatry 1997;54:839–846. [PubMed: 9294375]
29. Gaspar P, et al. The developmental role of serotonin: news from mouse molecular genetics. Nat Rev Neurosci 2003;4:1002–1012. [PubMed: 14618156]
30. Mejia JM, et al. Monoamine oxidase inhibition during brain development induces pathological aggressive behavior in mice. Biol Psychiatry 2002;52:811–821. [PubMed: 12372653]
31. Pattij T, Vanderschuren LJ. The neuropharmacology of impulsive behaviour. Trends Pharmacol Sci 2008;29:192–199. [PubMed: 18304658]
32. Turecki G, et al. Suicide and serotonin: study of variation at seven serotonin receptor genes in suicide completers. Am J Med Genet B Neuropsychiatr Genet 2003;118:36–40. [PubMed: 12627464]
33. Parellada M, et al. Is attempted suicide different in adolescent and adults? Psychiatry Res 2008;157:131–137. [PubMed: 17888518]

34. Conwell Y, et al. Age differences in behaviors leading to completed suicide. Am J Geriatr Psychiatry 1998;6:122–126. [PubMed: 9581207]
35. Wyder M, De Leo D. Behind impulsive suicide attempts: Indications from a community study. J Affect Disord 2007;104:167–173. [PubMed: 17397934]
36. Carlson GA. Early onset bipolar disorder: clinical and research considerations. J Clin Child Adolesc Psychol 2005;34:333–343. [PubMed: 15901234]
37. Joireman J, et al. The aggression paradox: understanding links among aggression, sensation seeking, and the consideration of future consequences. J Pers Soc Psychol 2003;84:1287–1302. [PubMed: 12793590]
38. Brent DA, et al. Familial pathways to early-onset suicide attempt: risk for suicidal behavior in offspring of mood-disordered suicide attempters. Arch Gen Psychiatry 2002;59:801–807. [PubMed: 12215079]
39. Isles AR, et al. Measuring impulsivity in mice using a novel operant delayed reinforcement task: effects of behavioural manipulations and d-amphetamine. Psychopharmacology (Berl) 2003;170:376–382. [PubMed: 12955301]
40. Snaith RP, Taylor CM. Irritability: definition, assessment and associated factors. Br J Psychiatry 1985;147:127–136. [PubMed: 3840045]
41. Conner KR, et al. The association of irritability and impulsivity with suicidal ideation among 15- to 20-year-old males. Suicide Life Threat Behav 2004;34:363–373. [PubMed: 15585458]
42. FDA. 2006. http://www.fda.org/cder/drug/antidepressants/MG_template.pdf
43. Leibenluft E, et al. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. J Child Adolesc Psychopharmacol 2006;16:456–466. [PubMed: 16958570]
44. Larson RW. Toward a psychology of positive youth development. Am Psychol 2000;55:170–183. [PubMed: 11392861]
45. Pine DS, et al. Adolescent fears as predictors of depression. Biol Psychiatry 2001;50:721–724. [PubMed: 11704080]
46. Koukopoulos A, et al. Mixed depressive states: nosologic and therapeutic issues. Int Rev Psychiatry 2005;17:21–37. [PubMed: 16194768]
47. Suzuki T, et al. Genetic differences in the development of physical dependence upon diazepam in Lewis and Fischer 344 inbred rat strains. Pharmacol Biochem Behav 1992;43:387–393. [PubMed: 1438478]
48. Einat H. Modelling facets of mania--new directions related to the notion of endophenotypes. J Psychopharmacol 2006;20:714–722. [PubMed: 16401660]
49. Meyer TD, Hautzinger M. The structure of affective symptoms in a sample of young adults. Compr Psychiatry 2003;44:110–116. [PubMed: 12658619]
50. Dalhouse AD. Social cohesiveness, hypersexuality and irritability induced by p-CPA in the rat. Physiol Behav 1976;17:679–686. [PubMed: 138145]
51. Ferrari F, et al. Does anxiety underly imidazole-induced behavioural effects in the rat? Psychopharmacology (Berl) 1989;99:345–351. [PubMed: 2594901]
52. Himmelsbach CK, et al. A method for testing addiction, tolerance and abstinence in the rat: results of its application to several morphine alcaloids. Pharmacol Exp Therap 1935;53:179–188.
53. Rasmussen K, et al. Opiate withdrawal and the rat locus coeruleus: behavioral, electrophysiological, and biochemical correlates. J Neurosci 1990;10:2308–2317. [PubMed: 2115910]
54. American Psychiatric Association. Diagnostic and statistical manual of mental disorders IV. Washington, DC: American Psychiatric Association; 1994.
55. Beevers CG, Miller IW. Perfectionism, cognitive bias, and hopelessness as prospective predictors of suicidal ideation. Suicide Life Threat Behav 2004;34:126–137. [PubMed: 15191269]
56. McGee R, et al. Low self-esteem and hopelessness in childhood and suicidal ideation in early adulthood. J Abnorm Child Psychol 2001;29:281–291. [PubMed: 11523834]
57. Maser JD, et al. Can temperament identify affectively ill patients who engage in lethal or near-lethal suicidal behavior? A 14-year prospective study. Suicide Life Threat Behav 2002;32:10–32. [PubMed: 11931008]

58. Beck AT, Weishaar ME. Suicide risk assessment and prediction. Crisis 1990;11:22–30. [PubMed: 2076612]
59. Seligman ME, Maier SF. Failure to escape traumatic shock. J Exp Psychol 1967;74:1–9. [PubMed: 6032570]
60. Anisman H, et al. Escape performance after inescapable shock in selectively bred lines of mice: response maintenance and catecholamine activity. J Comp Physiol Psychol 1979;93:229–241. [PubMed: 457947]
61. Henkel V, et al. Cognitive-behavioural theories of helplessness/hopelessness: valid models of depression? Eur Arch Psychiatry Clin Neurosci 2002;252:240–249. [PubMed: 12451467]
62. Popa D, et al. Lasting syndrome of depression produced by reduction in serotonin uptake during postnatal development: evidence from sleep, stress, and behavior. J Neurosci 2008;28:3546–3554. [PubMed: 18385313]
63. Panksepp, J. Affective neuroscience: the foundations of human and animal emotions. New York: Oxford University Press; 1998.
64. Fagen, R. Animal play behavior. New York: Oxford University Press; 1981.
65. Wommack JC, Delville Y. Stress, aggression, and puberty: neuroendocrine correlates of the development of agonistic behavior in golden hamsters. Brain Behav Evol 2007;70:267–273. [PubMed: 17914258]
66. Bizot JC, et al. Methylphenidate reduces impulsive behaviour in juvenile Wistar rats, but not in adult Wistar, SHR and WKY rats. Psychopharmacology (Berl) 2007;193:215–223. [PubMed: 17406857]
67. Leussis MP, Andersen SL. Is adolescence a sensitive period for depression? Behavioral and neuroanatomical findings from a social stress model. Synapse 2008;62:22–30. [PubMed: 17957735]
68. Badanich KA, et al. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. Eur J Pharmacol 2006;550:95–106. [PubMed: 17011546]
69. Adriani W, Laviola G. Elevated levels of impulsivity and reduced place conditioning with d-amphetamine: two behavioral features of adolescence in mice. Behav Neurosci 2003;117:695–703. [PubMed: 12931955]
70. Tsoory M, Richter-Levin G. Learning under stress in the adult rat is differentially affected by 'juvenile' or 'adolescent' stress. Int J Neuropsychopharmacol 2006;9:713–728. [PubMed: 16321169]
71. Kessler RC, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19. [PubMed: 8279933]
72. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 2008;33:88–109. [PubMed: 17851537]
73. Goodwin, FK.; Jamison, KR. Manic-depressive illness: bipolar disorders and recurrent depression. New York: Oxford University Press; 2007.
74. Dwivedi Y, et al. Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. Arch Gen Psychiatry 2003;60:273–282. [PubMed: 12622660]
75. Pellis SM, et al. The role of the cortex in play fighting by rats: developmental and evolutionary implications. Brain Behav Evol 1992;39:270–284. [PubMed: 1498649]
76. Isles AR, et al. Common genetic effects on variation in impulsivity and activity in mice. J Neurosci 2004;24:6733–6740. [PubMed: 15282276]
77. Irwin S. Comprehensive observational assessment: Ia. A systematic, quantitative procedure for assessing the behavioral and physiologic state of the mouse. Psychopharmacologia 1968;13:222–257. [PubMed: 5679627]
78. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature 2008;455:894–902. [PubMed: 18923511]

Fig 1.

In the resident intruder paradigm, a naive, weight- and age-matched mouse is placed into the home cage (a cage that the experimental mouse has been housed in for an extended period of time) of the test mouse (a), and the following behaviors are measured for a period of ten minutes: attack bites (b), tail rattling (c), wrestling (d), chasing behavior, and attack latency (see Table 1). [Figure 1b and 1c adapted from [75]].

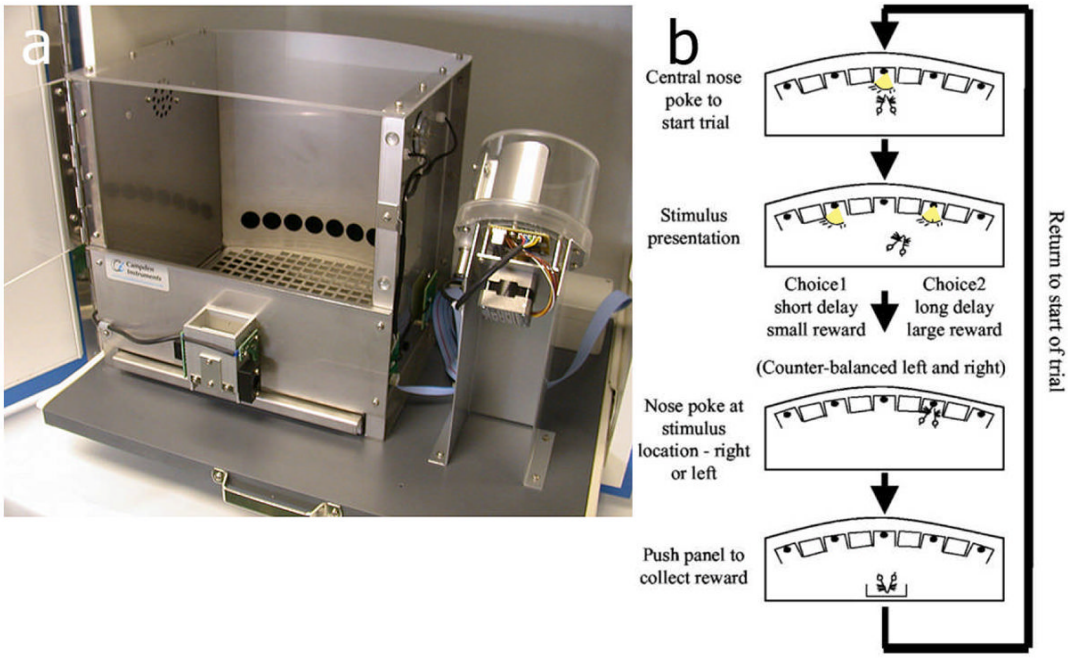

Fig 2.

Schematic displaying the 9-hole nose poke operant delayed reinforcement chamber (a) accompanied by a diagram displaying the delayed reward task (b). Table 1 contains a description of the task. [Photograph for Figure 1a taken from *Lafayette Instruments* web site: "Product 9-Hole Box for Rat and Mouse"; Figure 1b adapted from [76]].

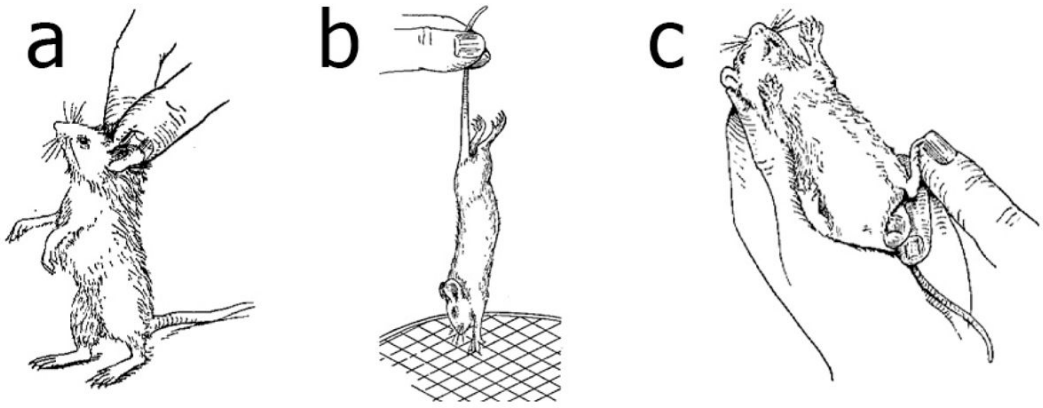

Fig 3.

In the image above, the animal is being tested for *positional passivity* (a), *positional struggle* (b), and struggle during *supine restraint* (c). When the animal is moderately restrained by the handler it will exhibit either a passive response or attempt to escape. The degree and duration of the struggling response can be quantified and is used as a measurement of irritability (See Table 1). [Figures 1a–c adapted from [77]].

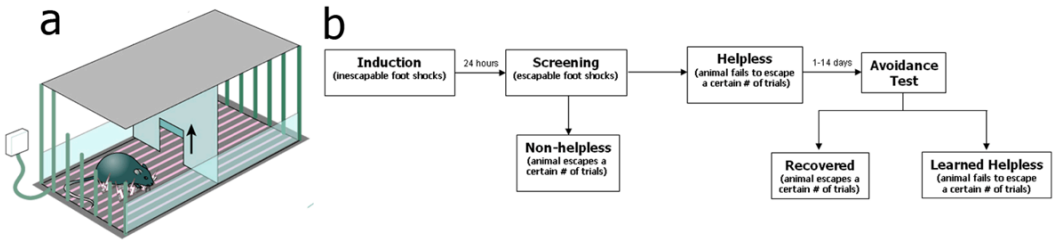

Fig 4.

A diagram depicting the learned helplessness screening/avoidance test is displayed above (a), along with a sample timeline for the learned helplessness procedure (b) (See Table 1) [Figure 1a adapted from [76,78]].

Table 1

Trait	Relevant Paradigm	Description	References
Aggression (Figure 1)	Resident Intruder	Various behavioral paradigms attempt to assess aggression in mice, but the Resident Intruder is the most frequently used. A naive, weight and age-matched mouse ("intruder") is placed into a cage that the experimental mouse has been housed in for an extended period of time (the "home-cage"), and the following behaviors are measured for a period of ten minutes: **Attack Bites**: Biting of the intruder mouse (Fig 1b) **Tail Rattling**: Rapid lateral quivering of the tail, just before or after attacking (Fig 1c) **Wrestling**: Vigorous shoving and sparring when both animals take on an upright posture; usually performed by both animals simultaneously (Fig 1d) **Chasing Behavior**: rapid pursuit of the intruder by the test male, with or without physical contact **Attack Latency**: Latency time to the first attack (in seconds) from the introduction of the intruder mouse. In animals that exhibit aggression, this measure can also be used to assess impulsivity.	[75]
Impulsivity (Figure 2)	Operant Delayed Reinforcement Task	Various behavioral paradigms attempt to assess impulsivity in mice, but the Operant Delayed Reinforcement Task is the most frequently used. This paradigm is based on the principle that a selection of smaller immediate gains is an "impulsive" choice, whereas the opposite bias is an index of "self control". Mice are first trained over a number of sessions to respond to a visual stimulus (light cue) with a nose-poke, and the associated panel pressing delivers food into the chamber. In the test, mice are trained to choose between two visual stimuli (a light cue presented on either the left or right side), one of which results in a small quantity of reinforcer (food), and the other resulting in a large quantity of reinforcer. As the session proceeds, a delay is introduced into the response (nose-poke) associated with the large reward. Thus, the nature of the choice is between a small but immediate quantity of reinforcer vs. a larger but delayed quantity of reinforcer (Fig 2).	[76]
Irritability (Figure 3)	Various Behavioral Paradigms	Various behavioral paradigms attempt to monitor irritability in mice. Two of the most frequently used are described below: **Resistance to Capture/Attempts to Struggle While Being Restrained**: Many of the tests used tomeasure irritability involve assessing rodent struggling behavior in response to human handling. As a response to moderate restraint applied by the handler, a mouse will either exhibit a passive or irritated response (Fig 3). The extent and duration of struggling behavior is used to measure irritability. **Responsiveness to Uncomfortable Stimuli**: These paradigms measure irritability as the responsiveness of an animal to a uniformly uncomfortable situation. In these paradigms, an uncomfortable stimulus is given (eg, such as a white bottle brush moving against the animal or a puff of air blown sharply through a straw onto the back of the animal's neck), and the animal's response is quantified. Animals that exhibit enhanced reactivity to the stimuli are considered to display irritable behavior.	[77]
Hopelessness/Helplessness (Figure 4)	Learned Helplessness Paradigm	This paradigm is based on the assumption that animals will normally try to escape an aversive stimulus (i.e. foot shock), but when the stimulus is inescapable, they will eventually stop trying to escape, exhibiting "despair-like" behavior. The paradigm is conducted over a time period ranging from a few days to two weeks, and is divided into three phases: induction, screening, and avoidance test. **Induction**: After a habituation period, the animal is given a number of foot shock trials from which it cannot escape. The number of trials and intensity of the shock varies. The duration between each shock trial is randomized and, in most cases, the shock is associated with a conditioned stimulus (light orauditory cue). **Screening**: Screening usually occurs the day after induction. It consists of a number of shock trials from which the animal can escape. If an animal fails to escape a certain number of trials, it is considered "helpless", otherwise it is deemed "non-helpless". Duration between shock trials is again randomized, though shock intensity and time window allotted for escape can vary. **Avoidance Test**: A number of days after screening, "helpless" animals are given an active avoidance test (see Fig 4). The test consists of a number of escapable shock trials. If an animal manages to escape a set number of trials, it is considered to have "recovered"; if it does not escape, it is considered to have "learned helplessness". In addition to number of escape failures, data on latency to escape are used to measure recovery.	[78]