Anxiety-related interventions in rodent defense behaviors: systematic review and meta-analyses

Authors

Farhan Mohammad[1], Joses Ho[2], Chun Lei Lim, Jia Hern Woo, Dennis Jun Jie Poon[2], Bhumika Lamba[2] & Adam Claridge-Chang[1, 2, 3, 4]

Affiliations

1. Program in Neuroscience and Behavioral Disorders, Duke-NUS Graduate Medical School, Singapore 138673

2. Institute for Molecular and Cell Biology, Agency for Science Technology and Research, Singapore 138673

3. Department of Physiology, National University of Singapore, Singapore 138673

4. Corresponding author: claridge-chang.adam@duke-nus.edu.sg

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ABSTRACT

Background

Assays measuring defense behavior in rodents, including the elevated plus maze, open field and light-dark box assays, have been widely used in preclinical models of anxiety to study the ability of therapeutic interventions to modulate the anxiety-like state. However, many important proposed anxiety-modulating factors, including genes, drugs and stressors have had paradoxical effects in these assays across different studies.

Objectives

We performed a systematic review and meta-analysis of the literature on the effect of anxiety-targeted interventions on rodent defense behaviors in three commonly-used assays: the elevated plus maze, open field and light-dark box assays. Our aim was to determine the effect sizes of a panel of purported anxiety-related interventions across three assays.

Data Sources

Using PubMed and EMBASE search phrases to identify articles, a systematic review was conducted on a panel of ten anxiety-linked interventions: diazepam, 5-HT1A receptor knockout and overexpression, SERT knockout and overexpression, pain, restraint, social isolation, corticotropin-releasing hormone and Crhr1. In addition, an *ad hoc* literature search was used to identify articles studying the effects of two genes that are not related to anxiety behaviours in rodents: adenylyl cyclase 1 and synaptotagmin.

Study Eligibility Criteria

Articles were included if they contained data on the effects of any one of the above-mentioned anxiety factors on one of the three rodent defense behaviors.

Synthesis Methods

Systematic meta-analyses were conducted; synthesis of the data was performed using random effects models of Hedges' *g*.

Results

Eight of the ten anxiety-related interventions had statistically significant effects on rodent defense behavior, while *Htr1a* overexpression and *Crh* knockout did not. Evidence for publication bias was found in three interventions: diazepam, *Htt* knockout, and social isolation.

Limitations

This meta-analysis excluded unpublished and non-English studies; publication bias and heterogeneity were identified in several meta-analyses.

Conclusions

The synthetic data support eight of the ten proposed anxiety factors as having moderate or large effects on rodent anxiety as measured by ARDEB assay (diazepam, *Htr1a* knockout, *Htr1a* overexpression, *Htt* knockout, *Htt* overexpression, pain, restraint and *Crhr1* knockout). Two interventions has small effects on rodent anxiety: social isolation and *Crh* knockout.

INTRODUCTION

The anxiety disorders are among the costliest classes of mental disorders, both in morbidity and economic cost (DiLuca and Olesen 2014; Baldwin *et al.* 2014). Development of anxiety-reducing (anxiolytic) drugs has been a major focus of the pharmaceutical industry and academic neuropsychiatric research, though no new drug types have been adopted since the introduction of selective serotonin uptake inhibitors (SSRIs) and other antidepressants for the treatment of anxiety disorders (Tone 2009; Griebel and Holmes 2013). Anxiety research relies on similarities between human emotional behavior and behaviors in animals (Darwin 1998), specifically rat and mouse (Prut and Belzung 2003). While there are many rodent behavioral paradigms that aim to model anxiety-like behaviors, three related assays that specifically aim to measure anxiety-related defense behavior (ARDEB) have been established, also referred to as the approach-avoidance conflict tests (Griebel and Holmes 2013). These assays are the elevated plus maze (EPM), the light-dark box (LD) and the open field (OF), the first, second and fifth most widely used assays in animal anxiety research, respectively (Griebel and Holmes 2013). All three arena types used in these assays contain a sheltered domain (e.g., the closed arms in EPM) and an exposed region. It is thought that avoidance of the exposed portions of the chamber reports on anxiety-like states in the rodent brain. These assays are generally accepted as preclinical assays of anxiety disorders, by reference to classic studies that validated them with a panel of drugs known to have anxiety-modulating effects in humans (Crawley and Goodwin 1980; Pellow *et al.* 1985; Simon, Dupuis, and Costentin 1994).

Rodent research has been implicated in the largely frustrated efforts to develop new types of anxiolytics (Griebel and Holmes 2013). The literature regarding defense behavior is contradictory about the size and even the direction of many interventions that are proposed to be anxiolytic or anxiogenic (together 'anxiotropic') (Prut and Belzung 2003; Griebel and Holmes 2013). This is true even for some anxiety-related genes with major clinical relevance, such as Htt, the target of SSRIs. As with the assessment of clinical anxiety interventions (Baldwin *et al.* 2014), a solid evidence base of the effect of 'mainstream' anxiety interventions in the rodent ARDEB assays is necessary to guide decisions about further basic research and therapeutic development (Vesterinen *et al.* 2014). In light of the widespread discordance, we aimed to conduct a quantitative review of some factors purported to influence rodent anxiety as measured by ARDEB. The primary aim of this study was to examine the validity of purported anxiety-influencing factors and to estimate

the magnitude of their effects on rodent anxiety. A secondary goal of this analysis were to examine patterns in ARDEB factor evidence: gaps in the literature, the extent of standardization/heterogeneity and publication bias. Establishing the validity of anxiety-targeted interventions might assist in understanding why these assays have not led to new therapies. Once identified by meta-analysis, effective anxiotropic interventions can be also adopted as benchmarks against which to validate new rodent assays and/or more genetically tractable model animal species (e.g. *Drosophila* and zebrafish).

METHODS

Literature review

Genes, drugs and environmental interventions that had been proposed to be involved in anxiety were identified by a literature search of review articles on the field of anxiety. Based on the history of anxiety research (Tone 2009; Griebel and Holmes 2013), a list of ten anxiotropic interventions were selected to be included in the systematic review, either due to their direct clinical importance (e.g., diazepam), their role as an example of a class of proposed anxiety-related factors (e.g., isolation), or their connection to a clinically important drug (e.g., Htt). A systematic review was conducted to identify published articles addressing experimental outcomes in rodents from the EPM, OF, or LD assays for these interventions. A comprehensive literature set for each genetic, pharmacological or environmental intervention was generated by a search on PubMed and EMBASE using specific search phrases (Table 1). The selective serotonin reuptake inhibitors (SSRIs) will be the subject of a separate study currently in preparation, due to their clinical importance (Baldwin *et al.* 2014), the very large number of studies conducted on them (Griebel and Holmes 2013), and their controversial efficacy (Kirsch *et al.* 2008).

Eligibility criteria and study selection

Bibliographic data (including study ID, date of publication, title and abstract) of studies identified in the systematic review were exported to a spreadsheet using the database export function. Each article on this list was then reviewed at four levels of detail (title, abstract, full text and a detailed review of experimental design) to determine their eligibility for the review. Studies were required to be written in English and to have reported ARDEB in adult rats or mice. We required that each included study contain (1) primary behavior data from either an OF, EPM, or LD experiment for the intervention of interest, (2) suitable controls were reported and (3) the relevant statistics were reported (mean, standard error or standard deviation, and sample sizes of both control and intervention groups). Since the focus of this study was the direct effects of anxiety-related interventions on ARDEB, experiments that used combination treatments were excluded. For drug and environmental interventions, possible confounding effects of the role of developmental stage were reduced by excluding studies not performed in adult rodents. For gene knockout and overexpression interventions, only experiments using a lifetime loss of function were included in the meta-analyses. We include all eligible studies in the meta-analysis (Table 1).

Selection of non-anxiety-related interventions

Studies of the effect of non-anxiety-related interventions on ARDEB were harder to find, perhaps due to the bias against publishing negative results, and/or reduced likelihood of mentioning them in abstracts. PubMed and EMBASE searches in this area failed to identify any useful studies. Instead, a conventional ad hoc literature search was used to find reports of the effects of adenylyl cyclase 1 (two articles) and synaptotagmin (one article) on anxiety-related behaviors.

Data items and extraction

The following data were collected from each of the included studies: authors, year of publication, figure and panel numbers, species, genotype, and mean, standard error of the mean and sample size (N) of each intervention and its related control group. Graphically presented data were extracted from Portable Document Format (PDF) files with the Measuring Tool in Adobe Acrobat Pro. All extracted data were checked by a second researcher. For values extracted from tables, the check consisted of ensuring the values were identical. For values extracted from graphical data (e.g. bar plots), the check consisted of a visual inspection to ensure that the value extracted with matched that of the graphical data. Any data discrepancy was reconciled by discussion and inspection by the original data extractor and the researcher who identified the discrepancy.

Summary measures

The following behavioral metrics were extracted from the articles: in OF studies, percent or total time spent at the center; in EPM studies, percent or total time spent on the open arm; in LD studies, percent or total time spent in the bright area. To synthesize these time-based metrics from the three assays, all estimates were standardized to Hedges' g, where g is a preferred variant of Cohen's d that uses the pooled standard deviation and is corrected for bias using Hedges' method (Cumming 2012; Borenstein *et al.* 2011). The conventional adjectives to describe effect size (trivial, small, moderate, large) are used where appropriate (Cumming 2012).

Synthesis of results

Meta-analyses of experimental outcomes, including the calculation of weighted mean effect sizes (Hedges' g), 95% confidence intervals, I^2 heterogeneity values, and p values using the random effects model, were performed with the metafor package in R (http://CRAN.R-project.org/package=metafor) (Viechtbauer 2010). All error bars in forest plots are 95%

confidence intervals; forest plots were generated with metafor and custom R scripts, and formatted in Adobe Illustrator.

Assessment of bias across studies

Publication bias was assessed using funnel plots and Egger's linear regression test for funnel plot asymmetry (Egger *et al.* 1997). The standard normal deviate (Hedges' g / standard error) for each study was regressed against the study's precision (1 / standard error) using the "lm" function in R (http://www.R-project.org/). For studies that had evidence of publication bias (p-value ≤ 0.05), the trim-and-fill method (Duval and Tweedie 2000) was employed to estimate the effects of publication bias on the effect size estimate. Funnel plots and trim-and-fill adjustments were performed with the 'metafor' package in R (Viechtbauer 2010).

RESULTS

Review selection criteria identified 298 eligible articles

The flow-chart in Figure 1 summarizes the study selection process. In total, 1155 articles were identified by the initial search in PubMed and EMBASE databases. According to the selection criteria described above, 500 studies were excluded based on their titles and a further 149 were excluded based on their abstracts. The full text of the remaining 506 articles were screened for criteria related to experimental paradigm, methods, and relevant variables, resulting in the exclusion of a further 224 studies. A total of 282 articles were considered eligible for inclusion in the review.

Characteristics of included experiments

The characteristics of all included studies are given in Table 3. In brief, 297 studies comprising 412 EPM experiments, 85 OF experiments and 86 LD experiments were identified. Studies were published between 1985 and 2015 and included data from 293 experiments conducted on mice and 287 experiments on rats. Studies reported 516 experiments conducted on male animals, 29 on female, 34 on mixed and 3 experiments with no gender information reported. ARDEB studies of diazepam used a median dosage of 1 mg/kg, with minimum and maximum dosages of 0.01 mg/kg and 20 mg/kg respectively. This dose range is similar to or higher than commonly used by patients.

Heterogeneity

Statistically significant heterogeneity was found in (8/10) of the meta-analyses. Only two meta-analyses had high heterogeneity (I^2 > 75%): *Htr1a* overexpression, and physical restraint (Higgins *et al.* 2003). Three of the meta-analyses, pain and *Htt* knockouts and diazepam, had moderate heterogeneity (50% < I^2 < 75%). Five meta-analyses had low heterogeneity (I^2 < 50%). As most of these syntheses contained data from more than one assay type, it is encouraging that half had low or moderate heterogeneity; this outcome is compatible with the idea that the three ARDEB assays are testing similar aspects of rodent anxiety.

Publication bias

Censorship of statistically non-significant experimental results and selective publication of statistically significant 'positive' results can cause a literature (and meta-analyses thereof)

to overstate effect sizes. For example, this effect (publication bias) has a profound influence on the literature on rodent models of stroke (Sena *et al.* 2010). Publication bias in the ARDEB literature was assessed for the six meta-analyses that had at least ten experiments (Table 2) (Sterne *et al.* 2011). Funnel plots of these data also showed pronounced asymmetry (Figure 2), a property that can arise from publication bias, the censorship of experiments showing small and/or statistically non-significant effect sizes (the file drawer effect) (Sterne *et al.* 2011). Egger's linear regression test for asymmetry revealed that three of these literatures showed statistically significant bias (Table 2). For the three biased data sets, we applied trim-and-fill adjustment to correct for the funnel plot asymmetry and to estimate the number of hypothesized missing studies (Duval and Tweedie 2000). We conclude that the literatures of diazepam, Htt knockout and social isolation effects on ARDEB are affected by publication bias.

Diazepam produces a moderate reduction in defense behaviors

Diazepam is an important minor tranquilizer that was used for several decades as the first line of treatment for anxiety disorders (Tone 2009) and, along with other benzodiazepines, is still used extensively to control anxiety (Baldwin *et al.* 2014). Recent clinical meta-analysis studies have found support for the efficacy of benzodiazepines in the short-term treatment of anxiety disorders (Baldwin *et al.* 2014). However, a published review of diazepam effects in open field studies revealed widespread disagreement between with 29 studies supporting an anxiolytic effect and 23 supporting either an anxiogenic effect or no effect (Prut and Belzung 2003). We reviewed the available literature on diazepam for the three major rodent ARDEB assays: EPM, OF and LD. This review identified 172 articles containing relevant data (de A Vieira *et al.* 2013; de Almeida *et al.* 2012; Assie *et al.* 1993; Bahi *et al.* 2014; Barbosa *et al.* 2008; Baretta *et al.* 2012; Barnes *et al.* 1990; Bellavite *et al.* 2011; Belzung and Agmo 1997; Bhatt *et al.* 2013; Bhattacharya and Mitra 1991; Birkett *et al.* 2011; Blainski *et al.* 2010; Borsini *et al.* 1993; Brioni *et al.* 1994; Carneiro *et al.* 2005; Carro-Juarez *et al.* 2012; de Castro *et al.* 2007; Cechin *et al.* 2003; Cha *et al.* 2005; Chen *et al.* 2005; Chen *et al.* 2004; Choleris *et al.* 2001; Cole and Rodgers 1995; Colla *et al.* 2015; Consoli *et al.* 2007; Contreras *et al.* 2011; Costa *et al.* 2011; Costall *et al.* 1990; Dalvi and Rodgers 2001; Dalvi and Rodgers 1999; de-Paris *et al.* 2000; Drapier *et al.* 2007; R. W. Dunn *et al.* 1998; R. W. Dunn, Corbett, and Fielding 1989; Ene *et al.* 2015; Engin, Treit, and Dickson 2009; Ennaceur *et al.* 2010; Fajemiroye *et al.* 2014; Faria *et al.* 1997; Faturi *et al.* 2010; F. Fernandez *et al.* 2004; S. P. Fernandez *et al.* 2008; Flores *et al.* 2006; Fortes *et al.*

2013; Fraser *et al.* 2010; Frassetto *et al.* 2010; Galeotti, Sanna, and Ghelardini 2013; Girish *et al.* 2013; Gomes *et al.* 2010; González-Pardo, Conejo, and Arias 2006; Ma Eva Gonzalez-Trujano *et al.* 2006; Maria Eva Gonzalez-Trujano *et al.* 2015; Griebel, Perrault, Tan, Schoemaker, and Sanger 1999b; Griebel, Perrault, Tan, Schoemaker, and Sanger 1999a; Griebel, Perrault, and Sanger 1998; Griebel, Perrault, and Sanger 1997; Griebel *et al.* 2002; Guilloux *et al.* 2013; Gupta *et al.* 2015; Gupta, Radhakrishnan, and Kurhe 2014; Han *et al.* 2009; Harada *et al.* 2006; Hasenohrl *et al.* 1996; Hazim *et al.* 2014; Huerta-Reyes *et al.* 2013; Hui *et al.* 2002; Ishaq 2014; N. S. Jain, Hirani, and Chopde 2005; Jastrzebska-Wiesek *et al.* 2014; Jászberényi *et al.* 2009; Jászberényi *et al.* 2007; Jessa *et al.* 1996; Jones *et al.* 1994; Kalouda and Pitsikas 2015; Karakas *et al.* 2011; Karim *et al.* 2011; Kebebew and Shibeshi 2013; Klodzinska, Tatarczynska, Stachowicz, *et al.* 2004; Klodzinska, Tatarczynska, Chojnacka-Wojcik, *et al.* 2004; Kong *et al.* 2006; Kumar and Bhat 2014; Kurhe *et al.* 2014; Kuribara *et al.* 2000; LaBuda and Fuchs 2001; Langen *et al.* 2005; Leggio *et al.* 2011; Lepicard *et al.* 2000; Jie Liu *et al.* 2015; Lolli *et al.* 2007; Mahendra and Bisht 2011; Mansouri *et al.* 2014; Martinez *et al.* 2006; Mechan *et al.* 2002; de Melo *et al.* 2006; Melo *et al.* 2010; Mesfin, Asres, and Shibeshi 2014; Meyer *et al.* 2013; Mi *et al.* 2005; Micale *et al.* 2009; Micale *et al.* 2008; Molander *et al.* 2011; Molina-Hernandez *et al.* 2004; Mora *et al.* 2005; Moreira *et al.* 2014; Nagaraja *et al.* 2012; Ochoa-Sanchez *et al.* 2012; Ognibene *et al.* 2008; Okuyama *et al.* 1999; Onusic *et al.* 2002; Pain *et al.* 1999; Paine, Jackman, and Olmstead 2002; Parent *et al.* 2012; Pellow *et al.* 1985; la Pena *et al.* 2013; Peng *et al.* 2004; Pires *et al.* 2013; Plaznik *et al.* 1994; Ponten *et al.* 2011; Popik *et al.* 2006; Radulovic *et al.* 2013; Rago *et al.* 1988; Ramanathan, Jaiswal, and Bhattacharya 1998; Raquibul Hasan *et al.* 2009; Rejon-Orantes *et al.* 2013; Rex, Morgenstern, and Fink 2002; Rochford *et al.* 1997; Saiyudthong and Marsden 2011; Sakaue *et al.* 2003; Santos Rosa *et al.* 2012; Satyan *et al.* 1998; Schmitt, Luddens, and Hiemke 2002; Schmitt, Luddens, and Hiemke 2001; Sherif *et al.* 1994; Da Silva *et al.* 1996; Silva *et al.* 2007; Simpson and Kelly 2012; Sorra *et al.* 2014; de Sousa *et al.* 2007; Srinivasan, Suresh, and Ramanathan 2003; Stankevicius *et al.* 2008; Stefanski *et al.* 1992; Steiner, Lecourt, and Jenck 2012; Stemmelin *et al.* 2008; Sugiyama *et al.* 2012; Swami *et al.* 2014; Taiwo *et al.* 2012; Tanaka, Satou, and Koike 2013; Tatarczynska *et al.* 2004; Thippeswamy *et al.* 2011; Thompson, Grabowski-Boase, and Tarantino 2015; Thongsaard *et al.* 1996; Tolardo *et al.* 2010; Varty *et al.* 2002; Venancio *et al.* 2011; Volke *et al.* 1998; Wada and Fukuda 1991; Wanasuntronwong *et al.* 2012; Wang *et al.* 2015; Wesolowska and Nikiforuk 2007; Wikinski *et al.* 2001; Wolfman *et al.* 1994; Yadav,

Kawale, and Nade 2008; Yamada *et al.* 2000; Yao *et al.* 2010; Yasumatsu *et al.* 1994; Zanoli *et al.* 2002; L.-M. Zhang *et al.* 2014; Zheng *et al.* 2009). Calculation of an average Hedges' *g* (Cumming 2012) for 386 experiments revealed that diazepam had a very large effect on ARDEB, with a -1.26 *g* [95CI -1.36, -1.17] reduction compared with untreated control animals (Figure 3, Table 2). However, as Egger's regression indicated the source literature was affected by publication bias, trim-and-fill correction indicated a smaller, but still large, effect of -0.85 *g* [95CI -0.74, -0.96]. The meta-analysis had a moderate level of heterogeneity, indicating that the assay type, laboratory, dosage, species, strain and other possible sources of experimental variation play a role in this literature.

5-HT1A receptor function influences ARDEB

Following negative publicity regarding the adverse effects of benzodiazepines (Tone 2009), pharmaceutical companies focused on the serotonergic system (Griebel and Holmes 2013). Of the fourteen mammalian serotonergic receptors, the serotonin receptor 5-HT1A has been targeted for its proposed connection with anxiety disorders and depression (Samuels *et al.* 2014). More than 1200 articles describe experiments connecting 5-HT1A agonism with rodent anxiety (Griebel and Holmes 2013). However, a substantial proportion of those articles reported that 5-HT1A agonists or knockout of the *Htr1a* gene either produced no effect on anxiety or an effect that was opposite to the receptor's proposed mode of action (Griebel and Holmes 2013). We performed systematic reviews of gene manipulations of *Htr1a* and identified 11 knockout articles (Piszczek *et al.* 2013; Vinkers *et al.* 2010; Gleason *et al.* 2010; Groenink *et al.* 2003; Klemenhagen *et al.* 2006; Freeman-Daniels, Beck, and Kirby 2011; A. Jain *et al.* 2012; Ramboz *et al.* 1998; Ferrés-Coy *et al.* 2013; Parks *et al.* 1998; Gross *et al.* 2002). Meta-analysis of the knockout data revealed that removal of *Htr1a* produced a moderate increase (Hedges' g = 0.73 [95CI 0.50, 0.96] , p = 3.5 x 10^{-10}) in ARDEB phenotypes (Figure 4A). The three studies of *Htr1a* overexpression found by the review (Kusserow *et al.* 2004; Bert *et al.* 2006; Audero *et al.* 2013) indicated that this intervention moderately decreased ARDEB (g = -0.6 [95CI -1.3, 0.13], p = 0.11; Figure 4B). The cumulative sample size of *Htr1a* overexpression is large (N = 100, 98), though the moderate effect size was not statistically significant and the heterogeneity was high (I^2 = 80%). These results confirm that *Htr1a* function has a moderate effect on rodent anxiety.

Anxiotropic effects of the serotonin transporter

The serotonin transporter (SERT) is the target for the selective serotonin reuptake inhibitors (SSRIs), a class of drugs used to treat depression and anxiety (Baldwin *et al.* 2014). Meta-

analysis of thirteen knockout studies (Holmes, Yang, *et al.* 2003; Holmes, Lit, *et al.* 2003; Lira *et al.* 2003; Li *et al.* 2004; Carroll *et al.* 2007; Kalueff *et al.* 2007; Olivier *et al.* 2008; Line *et al.* 2011; Schipper *et al.* 2011; Zhao *et al.* 2006; Kalueff, Jensen, and Murphy 2007; Moya *et al.* 2011; Pang *et al.* 2011) revealed a large anxiogenic effect (g = 0.88 [95CI 1.26, 0.23] , $p = 5.2 \times 10^{-14}$; Figure 5A) produced by knocking out the SERT gene, *Htt*. However, a funnel plot and Egger's regression revealed a pronounced bias in reported effect sizes (Egger's test $p = 6.7 \times 10^{-6}$, Table 2). Trim-and-fill adjustment filled the left segment of the funnel plot with ten imputed data points so as to obtain a symmetric funnel plot, reducing the effect size to g = 0.57 [95CI 0.29, 0.86], a moderate effect. Only two articles studying the effect of *Htt* overexpression on ARDEB were found (Jennings *et al.* 2006; Line *et al.* 2011). Meta-analysis revealed a large anxiolytic effect (g = -0.94 [95CI -1.69, -0.20], p = 0.013; Figure 5B) in EPM and OF assays (no LD articles were found). The transporter gene knockout and overexpression effects clearly connect *Htt* function to rodent anxiety. However, the direction of effects is the opposite of what would be expected from the clinical application of SERT inhibitors, given that SSRI reduction of SERT function is thought to have a therapeutic, anxiety-reducing effect.

The effects of environmental stressors in ARDEB

Environmental stressors have physiological effects on animals that promote the anxiety-like state (van Praag 2003). To survey a range of stress modalities we selected acute pain, bodily restraint and social isolation for review; all three have been found to promote anxiety in humans (Sherif and Oreland 1995).

The systematic review identified seven papers measuring the effect of acute pain on ARDEB (Yan Liu *et al.* 2015; Matsuzawa-Yanagida *et al.* 2008; Schellinck, Stanford, and Darrah 2003; Benbouzid *et al.* 2008; Parent *et al.* 2012; Leite-Almeida *et al.* 2012; Shang *et al.* 2014). Meta-analysis of the 21 experiments therein indicated a moderate anxiogenic effect (g = 0.56 [95CI 0.19, 0.93], $p = 2.9 \times 10^{-3}$; Figure 6A).

Review of 16 studies of rodent bodily restraint (Anand, Gulati, and Ray 2012; Busnardo *et al.* 2013; Carvajal *et al.* 2004; Chesworth *et al.* 2012; Estanislau and Morato 2005; Granjeiro *et al.* 2011; Harris *et al.* 2001; Joshi, Ray, and Gulati 2014; Jing Liu *et al.* 2011; Locchi *et al.* 2008; Lunga and Herbert 2004; Nosek *et al.* 2008; Ouagazzal *et al.* 2003; D. G. Reis *et al.* 2011; Rylkova *et al.* 2009; Walf and Frye 2012) containing 21 experiments indicated that it had an overall moderate anxiogenic effect in EPM and OF assays (g = 0.70 [95% CI 0.82 - 1.32], p = 0.027; Figure 6B). The restraint meta-analysis had a high level of

heterogeneity, I^2 = 89%; a subgroup analysis by assay type revealed that the different assays were not the source of this variability (data not shown).

The systematic review identified 50 articles on social isolation and ARDEB (Quintino-dos-Santos *et al.* 2014; Pisu *et al.* 2013; Linge, Pazos, and Diaz 2013; Xiao Liu *et al.* 2013; Yorgason *et al.* 2013; Chappell *et al.* 2013; Cuenya *et al.* 2012; Carrier and Kabbaj 2012; F. M. C. V. Reis *et al.* 2012; Y. Zhang *et al.* 2012; Yildirim, Erol, and Ulupinar 2012; Djordjevic *et al.* 2012; Workman *et al.* 2011; Hermes *et al.* 2011; Conrad *et al.* 2011; Bledsoe *et al.* 2011; Pisu *et al.* 2011; Kokare *et al.* 2010; Santos, de Andrade, and Graeff 2010; Ryu *et al.* 2009; H. Koike *et al.* 2009; Doremus-Fitzwater, Varlinskaya, and Spear 2009; McCool and Chappell 2009; Brenes, Padilla, and Fornaguera 2009; Lukkes *et al.* 2009; Imanaka *et al.* 2008; Leussis and Andersen 2008; Pritchard *et al.* 2008; Wei *et al.* 2007; Knuth and Etgen 2007; Estelles *et al.* 2007; Imanaka *et al.* 2006; Blakley and Pohorecky 2006; Thorsell *et al.* 2006; Hirani *et al.* 2005; Voikar *et al.* 2005; Abramov *et al.* 2004; Moragrega *et al.* 2003; Majercsik *et al.* 2003; Blednov *et al.* 2001; Lapiz *et al.* 2001; Cheeta, Irvine, and File 2001; Wright and Ingenito 2001; Haller, Halász, and Makara 2000; Serra *et al.* 2000; Haller and Halász 1999; Da Silva *et al.* 1996; Fone *et al.* 1996; Rodgers and Cole 1993; Das *et al.* 2014). Meta-analysis revealed a small anxiogenic effect (g = 0.33 [95CI 0.21, 0.44], p = 3.4 x 10^{-8}; Figure 6C). However, Egger's regression revealed funnel plot asymmetry, and the trim-and-fill method corrected the anxiogenic effect to only 0.21 g [95CI 0.07, 0.34], p = 3.1 x 10^{-3}) a very small anxiotropic effect (Figure 2B). It appears that, unlike the physical stressors, social isolation has only a modest influence on the ARDEB assays.

The role of CRH and its receptor on ARDEB

Several neuropeptide-related genes involved in stress signaling have been linked to anxiety, notably the peptide, corticotropin-releasing hormone (CRH; also known as corticotropin-releasing factor) (Kormos and Gaszner 2013) and its receptor, CRHR1. Two studies that examined the effects of *Crh* knockouts on ARDEB were found (Weninger *et al.* 1999), which revealed only a small effect (g = 0.30 [95CI -0.32, 0.92], p = 0.34; Figure 7A). This supports the idea that CRH has only a modest effect on the ARDEB; however, the meta-analytic result may suffer from insufficient precision as the cumulative sample size was only (N = 20, 21).

CRH exerts its biological action via two receptors known as CRHR1 and CRHR2. The two receptors are pharmacologically distinct and only the former has been widely studied in the context of anxiety (Owens and Nemeroff 1991; Paez-Pereda, Hausch, and

Holsboer 2011). Meta-analysis (Liebsch *et al.* 1995; Liebsch *et al.* 1999; Smith *et al.* 1998; Müller *et al.* 2003; Gammie and Stevenson 2006; Trimble *et al.* 2007) found that, in contrast to the *Crh* knockout, deletion of *Crhr1* had a large anxiolytic effect on ARDEB (g = -1.0 [95CI -1.30, -0.70], p = 6.64 x 10^{-11}; Figure 7B). The discordance between *Crh* and *Crhr1* knockout effects has previously been attributed to the action of other peptide ligand(s) of *Crhr1*, either urocortin or another, unidentified ligand (A. J. Dunn and Swiergiel 1999).

Genes with no purported effect on anxiety

Some of the interventions in the systematic review were found to have modest effects on ARDEB. We aimed to contextualize the magnitude of proposed anxiety factors with factors that the literature is not connected with anxiety. Such factors are not generally mentioned in anxiety reviews and it is difficult to identify them with database searches as they are less likely to be published or, when published, are unlikely to be the focus of a study and thus may not be mentioned in the abstract. We conducted an *ad hoc* search of the PubMed and EMBASE databases for systems unimportant to anxiety, which identified adenylyl cyclase 1 (Storm *et al.* 1998; Krishnan *et al.* 2008) and synaptotagmin 1 (Powell *et al.* 2004) as being proposed to have no anxiety-related activity. Meta-analyses confirmed that both interventions have very small (Hedges' g < 0.3) effects on ARDEB (Figure 8).

DISCUSSION

Summary of evidence

Inspection of the forest plots reveals that all of the primary publication sets include experimental effect sizes that are discordant, either in direction (anxiolytic versus anxiogenic) and/or magnitude. The generality of discordance in the literature emphasizes the utility of meta-analysis to behavioral neuroscience to give a quantitative overview and to synthesize the best evidence available. Of ten analyses of putative anxiotropic interventions, eight yielded at least moderate meta-analytic effect sizes and two produced small effect sizes (Figure 9). Of the moderate effect size factors, one (Htr1a overexpression) had a non-statistically significant test result. However, the majority of putative anxiety-related genes do have at least moderate effects on the rodent defense behaviors. The synthetic data strongly confirm that diazepam, the serotonergic system, environmental stressors, and *Crhr1* influence an anxiety-like process in the mouse brain.

Limitations

Some limitations of this study include that only published data were used and that only English language articles were used. Some studies had to be excluded from the meta-analysis during the full text scan because they did not report measures of variance. Only those studies were selected for meta-analysis which report time or percent time spent in exposed arena could be selected for meta-analysis. It is possible the inaccessible may affect the summary measures when added to the meta-analyses. The presence of publication bias in the three largest data sets assessed for bias, suggests that inclusion of further (e.g. unpublished) data to the smaller meta-analyses would be expected, on average,to lower these effect sizes as well. Heterogeneity was at least moderate ($I^2 > 50\%$) in five of the meta-analyses, indicating that the random effect model is insufficient to explain the variance in these data sets. Future work will include the implementation of mixed regression models that try to account for all or more of the unexplained variance.

Knowledge gaps, publication bias and heterogeneity

We found no knowledge gaps *per se,* as all the purported anxiety-related factors had at least two studies. Nevertheless, *Htt* overexpression, *Crh* knockouts and the non-anxiety genes had total experimental iterations below N = 64, 64, the sample size needed for 80% power to detect a 0.5 standard deviation effect size, indicating that more work could be done here. Of the six factors for which ≥ 20 studies were published, three were affected by

publication bias. Heterogeneity was high or moderate for five of the factors, and low for the other five factors reviewed, indicating that laboratory, strain, assay type and other protocol variations played a variable role across factors.

Htr1a interventions have weaker ARDEB effects than diazepam

Meta-analysis of *Htr1a* knockout and overexpression revealed that both have moderate anxiotropic effects. Both effects were smaller (0.73 and -0.6 *g* respectively) than the effect produced by diazepam (-0.85 *g*) suggesting that compounds aiming to increase 5-HT1A function may be a poor strategy to reduce anxiety, despite the pronounced *Htr1a* knockout outcome. This view is supported by recent clinical meta-analyses that have concluded that drugs targeting 5-HT1A - the azapirones - appear inferior to benzodiazepines for generalized anxiety disorder (Chessick *et al.* 2006) and that there is insufficient evidence to support azapirone use in panic disorder (Imai *et al.* 2014).

The Htt-SSRI paradox in defense behaviors

Drugs that target SERT, the SSRIs, are recommended as the first line of pharmacological treatment for anxiety (Baldwin *et al.* 2014). Blocking SERT-mediated transport (reuptake) of serotonin from the synaptic cleft is the proposed mechanism of SSRI anxiety reduction, although rodent studies of chronic SSRI effects on ARDEB have been inconclusive (Perez-Caballero *et al.* 2014; Griebel and Holmes 2013). Given the the inhibitors' clinical use, it is surprising that *Htt* knockouts have elevated anxiety relative to controls (0.57 *g*) and that *Htt* overexpression reduces rodent anxiety (-0.94 *g*).The reason for this discordance is not clear. In some cases the authors of the primary *Htt* knockout studies have not discussed this paradox (Moya *et al.* 2011; Schipper *et al.* 2011; Carroll *et al.* 2007; Kalueff *et al.* 2007). Other authors have remarked that the underlying reason remains unclear (Lira *et al.* 2003; Holmes, Yang, *et al.* 2003) or have called the validity of ARDEB assays into doubt (Pang *et al.* 2011). Primary study authors have also proposed two explanatory hypotheses. The first is that increased anxiety arises from developmental alterations present in *Htt* knockouts not present in chronically drug-treated animals (Olivier *et al.* 2008; Zhao *et al.* 2006; Holmes, Yang, *et al.* 2003). This hypothesis could be tested with conditional knockdown models, i.e. in animals with *Htt* only deleted at the adult stage. While systematic review of PubMed and EMBASE did not identify any published reports of post-developmental *Htt* knockout experiments (e.g., using floxed *Htt*), researchers have analyzed the anxiety-related effects of conditionally ablating the *Pet-1* gene. *Pet-1* is a transcription factor with an expression range that overlaps closely with the expression of *Htt*. In mice with *Pet-1* removed in

adulthood, mRNA levels of *Htt* are substantially reduced (Chen Liu *et al.* 2010). Like *Htt* knockouts, these mice show increased anxiety-like behaviors in multiple ARDEB assays (Chen Liu *et al.* 2010), eroding confidence in the developmental alteration hypothesis. A second hypothesis to explain the *Htt*/SSRI paradox is that there is a J-shaped relationship between *Htt* function and anxiety, i.e., both wild-type and knockout animals would have higher anxiety relative to animals with intermediate function (Olivier *et al.* 2008). Further study is required to fully understand the role of *Htt* and SSRIs in ARDEB.

Conclusions

This study supports the hypothesis that some mainstream anxiety-related interventions have trivial or unconfirmed effects in rodent defense behavior assays. However, this study also confirms a drug, two environmental stressors and a number of genes as authentic ARDEB influencers. These verified anxiety-related interventions (diazepam, *Htr1a* gene knockout, *Htt* gene knockout, *Htt* gene overexpression, acute pain, restraint and *Crhr1* gene knockout) can be used as reference manipulations to validate other animal models of anxiety-like behavior.

Meta-analysis has the ability to aggregate information and resolve discordance in the primary literature. This ability may be particularly useful in behavioral neuroscience where most primary articles describe experiments with low power (or precision) (Button *et al.* 2013). Precise estimation of effect magnitude is important both to build quantitative models of brain function and to improve the ability of preclinical studies to predict clinical efficacy.

Author Contributions

FM performed data extraction, systematic review, and meta-analyses and co-wrote the manuscript. CLL, JHW, DJJP and BL performed systematic review, and data extraction. JH did meta-analyses and publication bias analysis, performed data extraction checks, and contributed writing. ACC designed the study, guided the work, and wrote the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

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REFERENCES

Abramov, Urho, Sirli Raud, Sulev Kõks, Jürgen Innos, Kaido Kurrikoff, Toshimitsu Matsui, and Eero Vasar. 2004. "Targeted Mutation of CCK(2) Receptor Gene Antagonises Behavioural Changes Induced by Social Isolation in Female, but Not in Male Mice.." *Behavioural Brain Research* 155 (1): 1–11. doi:10.1016/j.bbr.2004.03.027.

Anand, Rashmi, Kavita Gulati, and Arunabha Ray. 2012. "Pharmacological Evidence for the Role of Nitric Oxide in the Modulation of Stress-Induced Anxiety by Morphine in Rats.." *European Journal of Pharmacology* 676 (1-3): 71–74. doi:10.1016/j.ejphar.2011.11.032.

Assie, M B, P Chopin, A Stenger, C Palmier, and M Briley. 1993. "Neuropharmacology of a New Potential Anxiolytic Compound, F 2692, 1-(3'-Trifluoromethyl Phenyl) 1,4-Dihydro 3-Amino 4-Oxo 6-Methyl Pyridazine. 1. Acute and in Vitro Effects.." *Psychopharmacology* 110 (1-2): 13–18.

Audero, Enrica, Boris Mlinar, Gilda Baccini, Zhiva K Skachokova, Renato Corradetti, and Cornelius Gross. 2013. "Suppression of Serotonin Neuron Firing Increases Aggression in Mice.." *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience* 33 (20): 8678–88. doi:10.1523/JNEUROSCI.2067-12.2013.

Bahi, Amine, Johannes Stephan Schwed, Miriam Walter, Holger Stark, and Bassem Sadek. 2014. "Anxiolytic and Antidepressant-Like Activities of the Novel and Potent Non-Imidazole Histamine H(3) Receptor Antagonist ST-1283.." *Drug Design, Development and Therapy* 8: 627–37.

Baldwin, David S, Ian M Anderson, David J Nutt, Christer Allgulander, Borwin Bandelow, Johan A den Boer, David M Christmas, *et al.* 2014. "Evidence-Based Pharmacological Treatment of Anxiety Disorders, Post-Traumatic Stress Disorder and Obsessive-Compulsive Disorder: a Revision of the 2005 Guidelines From the British Association for Psychopharmacology.." *Journal of Psychopharmacology (Oxford, England)* 28 (5): 403–39. doi:10.1177/0269881114525674.

Barbosa, Paulo R, Samira S Valvassori, Celso L Jr Bordignon, Virginia D Kappel, Marcio R Martins, Elaine C Gavioli, Joao Quevedo, and Flavio H Reginatto. 2008. "The Aqueous Extracts of Passiflora Alata and Passiflora Edulis Reduce Anxiety-Related Behaviors Without Affecting Memory Process in Rats.." *Journal of Medicinal Food* 11 (2): 282–88. doi:10.1089/jmf.2007.722.

Baretta, Irineia Paulina, Regiane Americo Felizardo, Vanessa Favero Bimbato, Maisa Goncalves Jorge dos Santos, Candida Aparecida Leite Kassuya, Arquimedes Gasparotto Junior, Cassia Regina da Silva, Sara Marchesan de Oliveira, Juliano Ferreira, and Roberto Andreatini. 2012. "Anxiolytic-Like Effects of Acute and Chronic Treatment with Achillea Millefolium L. Extract.." *Journal of Ethnopharmacology* 140 (1): 46–54. doi:10.1016/j.jep.2011.11.047.

Barnes, N M, B Costall, M E Kelly, E S Onaivi, and R J Naylor. 1990. "Ketotifen and Its Analogues Reduce Aversive Responding in the Rodent.." *Pharmacology Biochemistry and Behavior* 37 (4): 785–93.

Bellavite, Paolo, Paolo Magnani, Elisabetta Zanolin, and Anita Conforti. 2011. "Homeopathic Doses of Gelsemium Sempervirens Improve the Behavior of Mice in Response to Novel Environments.." *Evidence-Based Complementary and Alternative Medicine : eCAM* 2011: 362517.

Belzung, C, and A Agmo. 1997. "Naloxone Blocks Anxiolytic-Like Effects of Benzodiazepines in Swiss but Not in Balb/C Mice.." *Psychopharmacology* 132 (2): 195–201.

Benbouzid, Malika, Viviane Pallage, Mathieu Rajalu, Elisabeth Waltisperger, Stéphane

Doridot, Pierrick Poisbeau, Marie José Freund-Mercier, and Michel Barrot. 2008. "Sciatic Nerve Cuffing in Mice: a Model of Sustained Neuropathic Pain.." *European Journal of Pain (London, England)* 12 (5): 591–99. doi:10.1016/j.ejpain.2007.10.002.

Bert, Bettina, Heidrun Fink, Heide Hörtnagl, Rüdiger W Veh, Ben Davies, Franz Theuring, and Heike Kusserow. 2006. "Mice Over-Expressing the 5-HT(1A) Receptor in Cortex and Dentate Gyrus Display Exaggerated Locomotor and Hypothermic Response to 8-OH-DPAT.." *Behavioural Brain Research* 167 (2): 328–41. doi:10.1016/j.bbr.2005.09.020.

Bhatt, Shvetank, Radhakrishnan Mahesh, Thangaraj Devadoss, and Ankur Kumar Jindal. 2013. "Anxiolytic-Like Effect of (4-Benzylpiperazin-1-Yl)(3-Methoxyquinoxalin-2-Yl)Methanone (6g) in Experimental Mouse Models of Anxiety.." *Indian Journal of Pharmacology* 45 (3): 248–51.

Bhattacharya, S K, and S K Mitra. 1991. "Anxiolytic Activity of Panax Ginseng Roots: an Experimental Study.." *Journal of Ethnopharmacology* 34 (1): 87–92.

Birkett, Melissa A, Nina M Shinday, Eileen J Kessler, Jerrold S Meyer, Sarah Ritchie, and James K Rowlett. 2011. "Acute Anxiogenic-Like Effects of Selective Serotonin Reuptake Inhibitors Are Attenuated by the Benzodiazepine Diazepam in BALB/C Mice.." *Pharmacology Biochemistry and Behavior* 98 (4): 544–51. doi:10.1016/j.pbb.2011.03.006.

Blainski, Andressa, Vanessa K Piccolo, Joao Carlos P Mello, and Rubia M W de Oliveira. 2010. "Dual Effects of Crude Extracts Obtained From Petiveria Alliacea L. (Phytolaccaceae) on Experimental Anxiety in Mice.." *Journal of Ethnopharmacology* 128 (2): 541–44. doi:10.1016/j.jep.2010.01.012.

Blakley, Gregory, and Larissa A Pohorecky. 2006. "Psychosocial Stress Alters Ethanol's Effect on Open Field Behaviors.." *Pharmacology Biochemistry and Behavior* 84 (1): 51–61. doi:10.1016/j.pbb.2006.04.005.

Blednov, Y A, M Stoffel, S R Chang, and R A Harris. 2001. "GIRK2 Deficient Mice. Evidence for Hyperactivity and Reduced Anxiety.." *Physiology & Behavior* 74 (1-2): 109–17.

Bledsoe, Adam C, Kathryn M Oliver, Jamie L Scholl, and Gina L Forster. 2011. "Anxiety States Induced by Post-Weaning Social Isolation Are Mediated by CRF Receptors in the Dorsal Raphe Nucleus.." *Brain Research Bulletin* 85 (3-4): 117–22. doi:10.1016/j.brainresbull.2011.03.003.

Borenstein, M, L V Hedges, JPT Higgins, and H R Rothstein. 2011. *Introduction to Meta-Analysis*. John Wiley & Sons, Ltd.

Borsini, F, A Brambilla, R Cesana, and A Donetti. 1993. "The Effect of DAU 6215, a Novel 5HT-3 Antagonist, in Animal Models of Anxiety.." *Pharmacological Research* 27 (2): 151–64. doi:10.1006/phrs.1993.1015.

Brenes, Juan C, Michael Padilla, and Jaime Fornaguera. 2009. "A Detailed Analysis of Open-Field Habituation and Behavioral and Neurochemical Antidepressant-Like Effects in Postweaning Enriched Rats.." *Behavioural Brain Research* 197 (1): 125–37. doi:10.1016/j.bbr.2008.08.014.

Brioni, J D, A B O'Neill, D J Kim, M J Buckley, M W Decker, and S P Arneric. 1994. "Anxiolytic-Like Effects of the Novel Cholinergic Channel Activator ABT-418.." *The Journal of Pharmacology and Experimental Therapeutics* 271 (1): 353–61.

Busnardo, Cristiane, Fernando H F Alves, Carlos C Crestani, América A Scopinho, Leonardo B M Resstel, and Fernando M A Corrêa. 2013. "Paraventricular Nucleus of the Hypothalamus Glutamate Neurotransmission Modulates Autonomic, Neuroendocrine and Behavioral Responses to Acute Restraint Stress in Rats.." *European Neuropsychopharmacology : the Journal of the European College of Neuropsychopharmacology* 23 (11): 1611–22. doi:10.1016/j.euroneuro.2012.11.002.

Button, Katherine S, John P A Ioannidis, Claire Mokrysz, Brian A Nosek, Jonathan Flint, Emma S J Robinson, and Marcus R Munafò. 2013. “Power Failure: Why Small Sample Size Undermines the Reliability of Neuroscience..” *Nature Reviews Neuroscience* 14 (5): 365–76. doi:10.1038/nrn3475.

Carneiro, Lyvia M V, Joao Paulo L Diogenes, Silvania M M Vasconcelos, Gislei F Aragao, Emmanuelle C Noronha, Patricia B Gomes, and Glauce S B Viana. 2005. “Behavioral and Neurochemical Effects on Rat Offspring After Prenatal Exposure to Ethanol..” *Neurotoxicology and Teratology* 27 (4): 585–92. doi:10.1016/j.ntt.2005.06.006.

Carrier, Nicole, and Mohamed Kabbaj. 2012. “Testosterone and Imipramine Have Antidepressant Effects in Socially Isolated Male but Not Female Rats..” *Hormones and Behavior* 61 (5): 678–85. doi:10.1016/j.yhbeh.2012.03.001.

Carro-Juarez, Miguel, Juan Francisco Rodriguez-Landa, Maria de Lourdes Rodriguez-Pena, Maria de Jesus Rovirosa-Hernandez, and Francisco Garcia-Orduna. 2012. “The Aqueous Crude Extract of Montanoa Frutescens Produces Anxiolytic-Like Effects Similarly to Diazepam in Wistar Rats: Involvement of GABAA Receptor..” *Journal of Ethnopharmacology* 143 (2): 592–98. doi:10.1016/j.jep.2012.07.022.

Carroll, Jenna C, Janel M Boyce-Rustay, Rachel Millstein, Rebecca Yang, Lisa M Wiedholz, Dennis L Murphy, and Andrew Holmes. 2007. “Effects of Mild Early Life Stress on Abnormal Emotion-Related Behaviors in 5-HTT Knockout Mice..” *Behavior Genetics* 37 (1): 214–22. doi:10.1007/s10519-006-9129-9.

Carvajal, Cristina C, Freya Vercauteren, Yvan Dumont, Michael Michalkiewicz, and Rémi Quirion. 2004. “Aged Neuropeptide Y Transgenic Rats Are Resistant to Acute Stress but Maintain Spatial and Non-Spatial Learning..” *Behavioural Brain Research* 153 (2): 471–80. doi:10.1016/j.bbr.2004.01.004.

Cechin, E M, J Quevedo, T Barichello, R Machado-Vieira, V Gentil, and F Kapczinski. 2003. “Dose-Related Effects of Propericiazine in Rats..” *Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Médicas E Biológicas / Sociedade Brasileira De Biofísica [Et Al]* 36 (2): 227–31.

Cha, Hwa-Young, Jeong-Hill Park, Jin Tae Hong, Hwan-Soo Yoo, Sukgil Song, Bang-Yeon Hwang, Jae-Soon Eun, and Ki-Wan Oh. 2005. “Anxiolytic-Like Effects of Ginsenosides on the Elevated Plus-Maze Model in Mice..” *Biological & Pharmaceutical Bulletin* 28 (9): 1621–25.

Chappell, Ann M, Eugenia Carter, Brian A McCool, and Jeff L Weiner. 2013. “Adolescent Rearing Conditions Influence the Relationship Between Initial Anxiety-Like Behavior and Ethanol Drinking in Male Long Evans Rats..” *Alcoholism, Clinical and Experimental Research* 37 Suppl 1 (January): E394–403. doi:10.1111/j.1530-0277.2012.01926.x.

Cheeta, S, E Irvine, and S E File. 2001. “Social Isolation Modifies Nicotine's Effects in Animal Tests of Anxiety..” *British Journal of Pharmacology* 132 (7): 1389–95. doi:10.1038/sj.bjp.0703991.

Chen, Si Wei, Wei Xi Kong, Yi Jing Zhang, Yu Lei Li, Xiao Juan Mi, and Xiao Shuo Mu. 2004. “Possible Anxiolytic Effects of Taurine in the Mouse Elevated Plus-Maze..” *Life Sciences* 75 (12): 1503–11. doi:10.1016/j.lfs.2004.03.010.

Chen, Si Wei, Xiao Juan Mi, Rui Wang, Wen Juan Wang, Wei Xi Kong, Yi Jing Zhang, and Yu Lei Li. 2005. “Behavioral Effects of Sinomenine in Murine Models of Anxiety..” *Life Sciences* 78 (3): 232–38. doi:10.1016/j.lfs.2005.04.056.

Chessick, C A, M H Allen, Me Thase, A B C Batista Miralha da Cunha, F F K Kapczinski, M S M L de Lima, and J J S S dos Santos Souza. 2006. “Azapirones for Generalized Anxiety Disorder..” *Cochrane Database of Systematic Reviews (Online)*, no. 3: CD006115. doi:10.1002/14651858.CD006115.

Chesworth, Rose, Ernie Yulyaningsih, Emily Cappas, Jonathon Arnold, Amanda Sainsbury,

and Tim Karl. 2012. “The Response of Neuregulin 1 Mutant Mice to Acute Restraint Stress..” *Neuroscience Letters* 515 (1): 82–86. doi:10.1016/j.neulet.2012.03.024.

Choleris, E, A W Thomas, M Kavaliers, and F S Prato. 2001. “A Detailed Ethological Analysis of the Mouse Open Field Test: Effects of Diazepam, Chlordiazepoxide and an Extremely Low Frequency Pulsed Magnetic Field..” *Neuroscience and Biobehavioral Reviews* 25 (3): 235–60.

Cole, J C, and R J Rodgers. 1995. “Ethological Comparison of the Effects of Diazepam and Acute/Chronic Imipramine on the Behaviour of Mice in the Elevated Plus-Maze..” *Pharmacology Biochemistry and Behavior* 52 (3): 473–78.

Colla, Andre R S, Julia M Rosa, Mauricio P Cunha, and Ana Lucia S Rodrigues. 2015. “Anxiolytic-Like Effects of Ursolic Acid in Mice..” *European Journal of Pharmacology* 758 (July): 171–76. doi:10.1016/j.ejphar.2015.03.077.

Conrad, Kelly L, Katherine M Louderback, Caitlin P Gessner, and Danny G Winder. 2011. “Stress-Induced Alterations in Anxiety-Like Behavior and Adaptations in Plasticity in the Bed Nucleus of the Stria Terminalis..” *Physiology & Behavior* 104 (2): 248–56. doi:10.1016/j.physbeh.2011.03.001.

Consoli, Daniele, Gian Marco Leggio, Carmen Mazzola, Vincenzo Micale, and Filippo Drago. 2007. “Behavioral Effects of the Beta3 Adrenoceptor Agonist SR58611A: Is It the Putative Prototype of a New Class of Antidepressant/Anxiolytic Drugs?.” *European Journal of Pharmacology* 573 (1-3): 139–47. doi:10.1016/j.ejphar.2007.06.048.

Contreras, Carlos M, Juan Francisco Rodriguez-Landa, Ana G Gutierrez-Garcia, M Remedios Mendoza-Lopez, Rosa Isela Garcia-Rios, and Jonathan Cueto-Escobedo. 2011. “Anxiolytic-Like Effects of Human Amniotic Fluid and Its Fatty Acids in Wistar Rats..” *Behavioural Pharmacology* 22 (7): 655–62.

Costa, Celso A Rodrigues de Almeida, Daniele Oliveira Kohn, Valéria Martins de Lima, André Costa Gargano, Jorge Camilo Flório, and Mirtes Costa. 2011. “The GABAergic System Contributes to the Anxiolytic-Like Effect of Essential Oil From Cymbopogon Citratus (Lemongrass)..” *Journal of Ethnopharmacology* 137 (1): 828–36. doi:10.1016/j.jep.2011.07.003.

Costall, B, A M Domeney, P A Gerrard, Z P Horovitz, M E Kelly, R J Naylor, and D M Tomkins. 1990. “Effects of Captopril and SQ29,852 on Anxiety-Related Behaviours in Rodent and Marmoset..” *Pharmacology Biochemistry and Behavior* 36 (1): 13–20.

Crawley, J, and F K Goodwin. 1980. “Preliminary Report of a Simple Animal Behavior Model for the Anxiolytic Effects of Benzodiazepines..” *Pharmacology Biochemistry and Behavior* 13 (2): 167–70.

Cuenya, Lucas, Sandro Fosacheca, Alba Mustaca, and Giselle Kamenetzky. 2012. “Effects of Isolation in Adulthood on Frustration and Anxiety..” *Behavioural Processes* 90 (2): 155–60. doi:10.1016/j.beproc.2012.01.003.

Cumming, Geoff. 2012. *Understanding the New Statistics: Effect Sizes, Confidence Intervals, and Meta-Analysis*. *Multivariate Applications Series*. Vol. 1.

Da Silva, N L, V M Ferreira, A de P Carobrez, and G S Morato. 1996. “Individual Housing From Rearing Modifies the Performance of Young Rats on the Elevated Plus-Maze Apparatus..” *Physiology & Behavior* 60 (6): 1391–96.

Dalvi, A, and R J Rodgers. 1999. “Behavioral Effects of Diazepam in the Murine Plus-Maze: Flumazenil Antagonism of Enhanced Head Dipping but Not the Disinhibition of Open-Arm Avoidance..” *Pharmacology Biochemistry and Behavior* 62 (4): 727–34.

Dalvi, A, and R J Rodgers. 2001. “Anxiolytic Effects of Valproate and Diazepam in Mice Are Differentially Sensitive to Picrotoxin Antagonism..” *Pharmacology Biochemistry and Behavior* 68 (1): 23–32.

Darwin, Charles. 1998. *The Expression of the Emotions in Man and Animals*. Project

Gutenberg.

Das, Saroj Kumar, Kalpana Barhwal, Sunil Kumar Hota, Mahendra Kumar Thakur, and Ravi Bihari Srivastava. 2014. “Disrupting Monotony During Social Isolation Stress Prevents Early Development of Anxiety and Depression Like Traits in Male Rats..” *BMC Neuroscience* 16 (1): 2–2. doi:10.1186/s12868-015-0141-y.

de A Vieira, Larissa Fernanda, Maria Danielma dos S Reis, Altair Rogério A Brandão, Iana Mayane M N Viana, Juliane Pereira da Silva, Emiliano Barreto, and Salete Smaniotto. 2013. “Anxiolytic-Like Effect of the Extract From Bowdichia Virgilioides in Mice.” *Revista Brasileira De Farmacognosia* 23 (4): 680–86. doi:10.1590/S0102-695X2013005000044.

de Almeida, Antonia Amanda C, Jessica Pereira Costa, Rusbene Bruno F de Carvalho, Damiao Pergentino de Sousa, and Rivelilson Mendes de Freitas. 2012. “Evaluation of Acute Toxicity of a Natural Compound (+)-Limonene Epoxide and Its Anxiolytic-Like Action..” *Brain Research* 1448 (April): 56–62. doi:10.1016/j.brainres.2012.01.070.

de Castro, Pollyanna Celso F, Alberto Hoshino, Jair Campos da Silva, and Fulvio Rieli Mendes. 2007. “Possible Anxiolytic Effect of Two Extracts of Passiflora Quadrangularis L. in Experimental Models..” *Phytotherapy Research : PTR* 21 (5): 481–84. doi:10.1002/ptr.2079.

de Melo, Carla Thiciane Vasconcelos, Andreisa Paiva Monteiro, Caroline Porto Leite, Fernando Luiz Oliveira de Araujo, Vera Targino Moreira Lima, Jose Maria Barbosa-Filho, Marta Maria de Franca Fonteles, Silvania Maria Mendes de Vasconcelos, Glauce Socorro de Barros Viana, and Francisca Clea Florenco de Sousa. 2006. “Anxiolytic-Like Effects of (O-Methyl)-N-2,6-Dihydroxybenzoyl-Tyramine (Riparin III) From Aniba Riparia (Nees) Mez (Lauraceae) in Mice..” *Biological & Pharmaceutical Bulletin* 29 (3): 451–54.

de Sousa, Francisca Clea Florenco, Caroline Porto Leite, Carla Thiciane Vasconcelos de Melo, Fernando Luiz Oliveira de Araujo, Stanley Juan Chavez Gutierrez, Jose Maria Barbosa-Filho, Marta Maria de Franca Fonteles, Silvania Maria Mendes de Vasconcelos, and Glauce Socorro de Barros Viana. 2007. “Evaluation of Effects of N-(2-Hydroxybenzoyl) Tyramine (Riparin II) From Aniba Riparia (NEES) MEZ (Lauracea) in Anxiety Models in Mice..” *Biological & Pharmaceutical Bulletin* 30 (7): 1212–16.

de-Paris, F, J V Busnello, M R Vianna, J B Salgueiro, J Quevedo, I Izquierdo, and F Kapczinski. 2000. “The Anticonvulsant Compound Gabapentin Possesses Anxiolytic but Not Amnesic Effects in Rats..” *Behavioural Pharmacology* 11 (2): 169–73.

DiLuca, Monica, and Jes Olesen. 2014. “The Cost of Brain Diseases: a Burden or a Challenge?.” *Neuron* 82 (6). Elsevier Inc.: 1205–8. doi:10.1016/j.neuron.2014.05.044.

Djordjevic, Jelena, Ana Djordjevic, Miroslav Adzic, and Marija B Radojcic. 2012. “Effects of Chronic Social Isolation on Wistar Rat Behavior and Brain Plasticity Markers..” *Neuropsychobiology* 66 (2): 112–19. doi:10.1159/000338605.

Doremus-Fitzwater, Tamara L, Elena I Varlinskaya, and Linda Patia Spear. 2009. “Effects of Pretest Manipulation on Elevated Plus-Maze Behavior in Adolescent and Adult Male and Female Sprague-Dawley Rats..” *Pharmacology Biochemistry and Behavior* 92 (3): 413–23. doi:10.1016/j.pbb.2009.01.006.

Drapier, Dominique, Daniele Bentue-Ferrer, Bruno Laviolle, Bruno Millet, Herve Allain, Michel Bourin, and Jean-Michel Reymann. 2007. “Effects of Acute Fluoxetine, Paroxetine and Desipramine on Rats Tested on the Elevated Plus-Maze..” *Behavioural Brain Research* 176 (2): 202–9. doi:10.1016/j.bbr.2006.10.002.

Dunn, A J, and A H Swiergiel. 1999. “Behavioral Responses to Stress Are Intact in CRF-Deficient Mice..” *Brain Research* 845 (1): 14–20.

Dunn, R W, R Corbett, and S Fielding. 1989. “Effects of 5-HT1A Receptor Agonists and NMDA Receptor Antagonists in the Social Interaction Test and the Elevated Plus

Maze.." *European Journal of Pharmacology* 169 (1): 1–10.
Dunn, R W, T A Reed, P D Copeland, and C A Frye. 1998. "The Nitric Oxide Synthase Inhibitor 7-Nitroindazole Displays Enhanced Anxiolytic Efficacy Without Tolerance in Rats Following Subchronic Administration.." *Neuropharmacology* 37 (7): 899–904.
Duval, S, and R Tweedie. 2000. "Trim and Fill: a Simple Funnel-Plot-Based Method of Testing and Adjusting for Publication Bias in Meta-Analysis.." *Biometrics* 56 (2): 455–63.
Egger, M, G Davey Smith, M Schneider, and C Minder. 1997. "Bias in Meta-Analysis Detected by a Simple, Graphical Test.." *BMJ (Clinical Research Ed.)* 315 (7109): 629–34.
Ene, Hila M, Nirit Z Kara, Noa Barak, Tal Reshef Ben-Mordechai, and Haim Einat. 2015. "Effects of Repeated Asenapine in a Battery of Tests for Anxiety-Like Behaviours in Mice.." *Acta Neuropsychiatrica*, September, 1–7. doi:10.1017/neu.2015.53.
Engin, E, D Treit, and C T Dickson. 2009. "Anxiolytic- and Antidepressant-Like Properties of Ketamine in Behavioral and Neurophysiological Animal Models.." *Neuroscience* 161 (2): 359–69. doi:10.1016/j.neuroscience.2009.03.038.
Ennaceur, A, S Michalikova, R van Rensburg, and P L Chazot. 2010. "Distinguishing Anxiolysis and Hyperactivity in an Open Space Behavioral Test.." *Behavioural Brain Research* 207 (1): 84–98. doi:10.1016/j.bbr.2009.09.042.
Estanislau, Celio, and Silvio Morato. 2005. "Prenatal Stress Produces More Behavioral Alterations Than Maternal Separation in the Elevated Plus-Maze and in the Elevated T-Maze.." *Behavioural Brain Research* 163 (1): 70–77. doi:10.1016/j.bbr.2005.04.003.
Estelles, Josefina, Javier Lluch, Marta Rodriguez-Arias, Maria A Aguilar, and Jose Minarro. 2007. "Cocaine Exposure During Adolescence Affects Anxiety in Adult Mice.." *Brain Research Bulletin* 71 (4): 393–403. doi:10.1016/j.brainresbull.2006.10.008.
Fajemiroye, James O, Pablinny M Galdino, Iziara F Florentino, Fabio F Da Rocha, Paulo C Ghedini, Prabhakar R Polepally, Jordan K Zjawiony, and Elson A Costa. 2014. "Plurality of Anxiety and Depression Alteration Mechanism by Oleanolic Acid.." *Journal of Psychopharmacology (Oxford, England)* 28 (10): 923–34. doi:10.1177/0269881114536789.
Faria, M S, M N Muscará, H Moreno Júnior, S A Teixeira, H B Dias, B De Oliveira, F G Graeff, and G De Nucci. 1997. "Acute Inhibition of Nitric Oxide Synthesis Induces Anxiolysis in the Plus Maze Test.." *European Journal of Pharmacology* 323 (1): 37–43.
Faturi, Claudia Brito, Jose Roberto Leite, Pericles Barreto Alves, Adriane Conte Canton, and Flavia Teixeira-Silva. 2010. "Anxiolytic-Like Effect of Sweet Orange Aroma in Wistar Rats.." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 34 (4): 605–9. doi:10.1016/j.pnpbp.2010.02.020.
Fernandez, Fabian, Michael A Misilmeri, Jennifer C Felger, and Darragh P Devine. 2004. "Nociceptin/Orphanin FQ Increases Anxiety-Related Behavior and Circulating Levels of Corticosterone During Neophobic Tests of Anxiety.." *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 29 (1): 59–71. doi:10.1038/sj.npp.1300308.
Fernandez, Sebastian P, Kenneth N Mewett, Jane R Hanrahan, Mary Chebib, and Graham A R Johnston. 2008. "Flavan-3-Ol Derivatives Are Positive Modulators of GABA(a) Receptors with Higher Efficacy for the Alpha(2) Subtype and Anxiolytic Action in Mice.." *Neuropharmacology* 55 (5): 900–907. doi:10.1016/j.neuropharm.2008.06.069.
Ferrés-Coy, Albert, Noemí Santana, Anna Castañé, Roser Cortés, María C Carmona, Miklos Toth, Andrés Montefeltro, Francesc Artigas, and Analía Bortolozzi. 2013. "Acute 5-HT(1)a Autoreceptor Knockdown Increases Antidepressant Responses and Serotonin Release in Stressful Conditions.." *Psychopharmacology* 225 (1): 61–74.

doi:10.1007/s00213-012-2795-9.

Flores, Juan A, Beatriz Galan-Rodriguez, Susana Ramiro-Fuentes, and Emilio Fernandez-Espejo. 2006. “Role for Dopamine Neurons of the Rostral Linear Nucleus and Periaqueductal Gray in the Rewarding and Sensitizing Properties of Heroin..” *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 31 (7): 1475–88. doi:10.1038/sj.npp.1300946.

Fone, K C, K Shalders, Z D Fox, R Arthur, and C A Marsden. 1996. “Increased 5-HT2C Receptor Responsiveness Occurs on Rearing Rats in Social Isolation..” *Psychopharmacology* 123 (4): 346–52.

Fortes, Amanda C, Antonia Amanda C Almeida, Francisco Jaime B Mendonca-Junior, Rivelilson M Freitas, Jose Lamartine Soares-Sobrinho, and Monica Felts de La Roca Soares. 2013. “Anxiolytic Properties of New Chemical Entity, 5TIO1..” *Neurochemical Research* 38 (4): 726–31. doi:10.1007/s11064-013-0970-y.

Fraser, Leanne M, Richard E Brown, Ahmed Hussin, Mara Fontana, Ashley Whittaker, Timothy P O'Leary, Lauren Lederle, Andrew Holmes, and Andre Ramos. 2010. “Measuring Anxiety- and Locomotion-Related Behaviours in Mice: a New Way of Using Old Tests..” *Psychopharmacology* 211 (1): 99–112. doi:10.1007/s00213-010-1873-0.

Frassetto, Silvana S, Isis O Alves, Marislane M Santos, Ana E S Schmidt, Janaína J Lopes, Paulo A Oliveira, Anapaula S Vinagre, and Patrícia Pereira. 2010. “Absence of Sibutramine Effect on Spontaneous Anxiety in Rats..” *Arquivos Brasileiros De Endocrinologia E Metabologia* 54 (4): 375–80.

Freeman-Daniels, Emily, Sheryl G Beck, and Lynn G Kirby. 2011. “Cellular Correlates of Anxiety in CA1 Hippocampal Pyramidal Cells of 5-HT1A Receptor Knockout Mice..” *Psychopharmacology* 213 (2-3): 453–63. doi:10.1007/s00213-010-2030-5.

Galeotti, Nicoletta, Maria Domenica Sanna, and Carla Ghelardini. 2013. “Pleiotropic Effect of Histamine H4 Receptor Modulation in the Central Nervous System..” *Neuropharmacology* 71 (August): 141–47. doi:10.1016/j.neuropharm.2013.03.026.

Gammie, Stephen C, and Sharon A Stevenson. 2006. “Intermale Aggression in Corticotropin-Releasing Factor Receptor 1 Deficient Mice..” *Behavioural Brain Research* 171 (1): 63–69. doi:10.1016/j.bbr.2006.03.017.

Girish, Chandrashekaran, Vishnu Raj, Jayasree Arya, and Sadasivam Balakrishnan. 2013. “Involvement of the GABAergic System in the Anxiolytic-Like Effect of the Flavonoid Ellagic Acid in Mice..” *European Journal of Pharmacology* 710 (1-3): 49–58. doi:10.1016/j.ejphar.2013.04.003.

Gleason, G, B Liu, S Bruening, B Zupan, A Auerbach, W Mark, J E Oh, J Gal-Toth, F Lee, and M Toth. 2010. “The serotonin1A Receptor Gene as a Genetic and Prenatal Maternal Environmental Factor in Anxiety..” *Proceedings of the National Academy of Sciences of the United States of America* 107 (16): 7592–97. doi:10.1073/pnas.0914805107.

Gomes, Patricia Bezerra, Mariana Lima Feitosa, Maria Izabel Gomes Silva, Emmanuelle Coelho Noronha, Brinell Arcanjo Moura, Edith Teles Venancio, Emiliano Ricardo Vasconcelos Rios, *et al.* 2010. “Anxiolytic-Like Effect of the Monoterpene 1,4-Cineole in Mice..” *Pharmacology Biochemistry and Behavior* 96 (3): 287–93. doi:10.1016/j.pbb.2010.05.019.

Gonzalez-Trujano, Ma Eva, Ana Laura Martinez, Adelfo Reyes-Ramirez, Benito Reyes-Trejo, and Andres Navarrete. 2006. “Palmitone Isolated From Annona Diversifolia Induces an Anxiolytic-Like Effect in Mice..” *Planta Medica* 72 (8): 703–7. doi:10.1055/s-2006-931598.

Gonzalez-Trujano, Maria Eva, Hilda Ponce-Munoz, Sergio Hidalgo-Figueroa, Gabriel Navarrete-Vazquez, and Samuel Estrada-Soto. 2015. “Depressant Effects of Agastache

Mexicana Methanol Extract and One of Major Metabolites Tilianin.." *Asian Pacific Journal of Tropical Medicine* 8 (3): 185–90. doi:10.1016/S1995-7645(14)60312-6.

González-Pardo, Héctor, Nélida M Conejo, and Jorge L Arias. 2006. "Oxidative Metabolism of Limbic Structures After Acute Administration of Diazepam, Alprazolam and Zolpidem.." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 30 (6): 1020–26. doi:10.1016/j.pnpbp.2006.03.026.

Granjeiro, Erica M, Felipe V Gomes, Francisco S Guimarães, Fernando M A Corrêa, and Leonardo B M Resstel. 2011. "Effects of Intracisternal Administration of Cannabidiol on the Cardiovascular and Behavioral Responses to Acute Restraint Stress.." *Pharmacology Biochemistry and Behavior* 99 (4): 743–48. doi:10.1016/j.pbb.2011.06.027.

Griebel, G, G Perrault, and D J Sanger. 1997. "CCK Receptor Antagonists in Animal Models of Anxiety: Comparison Between Exploration Tests, Conflict Procedures and a Model Based on Defensive Behaviours.." *Behavioural Pharmacology* 8 (6-7): 549–60.

Griebel, G, G Perrault, and D J Sanger. 1998. "Characterization of the Behavioral Profile of the Non-Peptide CRF Receptor Antagonist CP-154,526 in Anxiety Models in Rodents. Comparison with Diazepam and Buspirone.." *Psychopharmacology* 138 (1): 55–66.

Griebel, G, G Perrault, S Tan, H Schoemaker, and D J Sanger. 1999a. "Pharmacological Studies on Synthetic Flavonoids: Comparison with Diazepam.." *Neuropharmacology* 38 (7): 965–77.

Griebel, G, G Perrault, S Tan, H Schoemaker, and D J Sanger. 1999b. "Comparison of the Pharmacological Properties of Classical and Novel BZ-Omega Receptor Ligands.." *Behavioural Pharmacology* 10 (5): 483–95.

Griebel, Guy, and Andrew Holmes. 2013. "50 Years of Hurdles and Hope in Anxiolytic Drug Discovery.." *Nat Rev Drug Discov* 12 (9): 667–87. doi:10.1038/nrd4075.

Griebel, Guy, Jacques Simiand, Regis Steinberg, Mireille Jung, Danielle Gully, Pierre Roger, Michel Geslin, Bernard Scatton, Jean-Pierre Maffrand, and Philippe Soubrie. 2002. "4-(2-Chloro-4-Methoxy-5-Methylphenyl)-N-[(1S)-2-Cyclopropyl-1-(3-Fluoro-4-Methylp Henyl)Ethyl]5-Methyl-N-(2-Propynyl)-1, 3-Thiazol-2-Amine Hydrochloride (SSR125543A), a Potent and Selective Corticotrophin-Releasing Factor(1) Receptor Antagonist. II. Characterization in Rodent Models of Stress-Related Disorders.." *The Journal of Pharmacology and Experimental Therapeutics* 301 (1): 333–45.

Groenink, Lucianne, Tommy Pattij, Reinoud De Jongh, Jan Van der Gugten, Ronald S Oosting, Anneloes Dirks, and Berend Olivier. 2003. "5-HT1A Receptor Knockout Mice and Mice Overexpressing Corticotropin-Releasing Hormone in Models of Anxiety.." *European Journal of Pharmacology* 463 (1-3): 185–97. doi:10.1016/S0014-2999(03)01281-0.

Gross, Cornelius, Xiaoxi Zhuang, Kimberly Stark, Sylvie Ramboz, Ronald Oosting, Lynn Kirby, Luca Santarelli, Sheryl Beck, and René Hen. 2002. "Serotonin1A Receptor Acts During Development to Establish Normal Anxiety-Like Behaviour in the Adult.." *Nature* 416 (6879): 396–400. doi:10.1038/416396a.

Guilloux, Jean-Philippe, Indira Mendez-David, Alan Pehrson, Bruno P Guiard, Christelle Repérant, Sophie Orvoen, Alain M Gardier, *et al.* 2013. "Antidepressant and Anxiolytic Potential of the Multimodal Antidepressant Vortioxetine (Lu AA21004) Assessed by Behavioural and Neurogenesis Outcomes in Mice.." *Neuropharmacology* 73 (October): 147–59. doi:10.1016/j.neuropharm.2013.05.014.

Gupta, Deepali, Mahesh Radhakrishnan, and Yeshwant Kurhe. 2014. "Anxiolytic-Like Effects of Alverine Citrate in Experimental Mouse Models of Anxiety.." *European Journal of Pharmacology* 742 (November): 94–101. doi:10.1016/j.ejphar.2014.08.033.

Gupta, Deepali, Mahesh Radhakrishnan, Devadoss Thangaraj, and Yeshwant Kurhe. 2015.

"Pharmacological Evaluation of Novel 5-HT3 Receptor Antagonist, QCM-13 (N-Cyclohexyl-3-Methoxyquinoxalin-2-Carboxamide) as Anti-Anxiety Agent in Behavioral Test Battery.." *Journal of Pharmacy & Bioallied Sciences* 7 (2): 103–8.

Haller, J, and J Halász. 1999. "Mild Social Stress Abolishes the Effects of Isolation on Anxiety and Chlordiazepoxide Reactivity.." *Psychopharmacology* 144 (4): 311–15.

Haller, J, J Halász, and G B Makara. 2000. "Housing Conditions and the Anxiolytic Efficacy of Buspirone: the Relationship Between Main and Side Effects.." *Behavioural Pharmacology* 11 (5): 403–12.

Han, Huishan, Yuan Ma, Jae-Soon Eun, Rihua Li, Jin Tae Hong, Myung-Koo Lee, and Ki-Wan Oh. 2009. "Anxiolytic-Like Effects of Sanjoinine a Isolated From Zizyphi Spinosi Semen: Possible Involvement of GABAergic Transmission.." *Pharmacology Biochemistry and Behavior* 92 (2): 206–13. doi:10.1016/j.pbb.2008.11.012.

Harada, Katsuya, Masaki Aota, Tatsuo Inoue, Ritsuko Matsuda, Takuma Mihara, Takayuki Yamaji, Koji Ishibashi, and Nobuya Matsuoka. 2006. "Anxiolytic Activity of a Novel Potent Serotonin 5-HT2C Receptor Antagonist FR260010: a Comparison with Diazepam and Buspirone.." *European Journal of Pharmacology* 553 (1-3): 171–84. doi:10.1016/j.ejphar.2006.09.042.

Harris, R B, J Zhou, M Shi, S Redmann, R L Mynatt, and D H Ryan. 2001. "Overexpression of Agouti Protein and Stress Responsiveness in Mice.." *Physiology & Behavior* 73 (4): 599–608.

Hasenohrl, R U, C H Nichau, C H Frisch, M A De Souza Silva, J P Huston, C M Mattern, and R Hacker. 1996. "Anxiolytic-Like Effect of Combined Extracts of Zingiber Officinale and Ginkgo Biloba in the Elevated Plus-Maze.." *Pharmacology Biochemistry and Behavior* 53 (2): 271–75.

Hazim, Ammar Imad, Surash Ramanathan, Suhanya Parthasarathy, Mustapha Muzaimi, and Sharif Mahsufi Mansor. 2014. "Anxiolytic-Like Effects of Mitragynine in the Open-Field and Elevated Plus-Maze Tests in Rats.." *The Journal of Physiological Sciences : JPS* 64 (3): 161–69. doi:10.1007/s12576-014-0304-0.

Hermes, Gretchen, Nanxin Li, Catharine Duman, and Ronald Duman. 2011. "Post-Weaning Chronic Social Isolation Produces Profound Behavioral Dysregulation with Decreases in Prefrontal Cortex Synaptic-Associated Protein Expression in Female Rats.." *Physiology & Behavior* 104 (2): 354–59. doi:10.1016/j.physbeh.2010.12.019.

Higgins, JPT, S G Thompson, J J Deeks, and Douglas G Altman. 2003. "Measuring Inconsistency in Meta-Analyses." *BMJ: British Medical Journal* 327: 557–60.

Hirani, Khemraj, Ajay N Sharma, Nishant S Jain, Rajesh R Ugale, and Chandrabhan T Chopde. 2005. "Evaluation of GABAergic Neuroactive Steroid 3alpha-Hydroxy-5alpha-Pregnane-20-One as a Neurobiological Substrate for the Anti-Anxiety Effect of Ethanol in Rats.." *Psychopharmacology* 180 (2): 267–78. doi:10.1007/s00213-005-2169-7.

Holmes, A, Q Lit, D L Murphy, E Gold, and J N Crawley. 2003. "Abnormal Anxiety-Related Behavior in Serotonin Transporter Null Mutant Mice: the Influence of Genetic Background.." *Genes, Brain, and Behavior* 2 (6): 365–80.

Holmes, Andrew, Rebecca J Yang, Klaus-Peter Lesch, Jacqueline N Crawley, and Dennis L Murphy. 2003. "Mice Lacking the Serotonin Transporter Exhibit 5-HT(1A) Receptor-Mediated Abnormalities in Tests for Anxiety-Like Behavior.." *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 28 (12): 2077–88. doi:10.1038/sj.npp.1300266.

Huerta-Reyes, Maira, Maribel Herrera-Ruiz, Manases Gonzalez-Cortazar, Alejandro Zamilpa, Esther Leon, Ricardo Reyes-Chilpa, Arturo Aguilar-Rojas, and Jaime Tortoriello. 2013. "Neuropharmacological in Vivo Effects and Phytochemical Profile of the Extract From the Aerial Parts of Heteropterys Brachiata (L.) DC. (Malpighiaceae).."

Journal of Ethnopharmacology 146 (1): 311–17. doi:10.1016/j.jep.2012.12.049.

Hui, Kwok Min, Michael S Y Huen, Hong Yan Wang, Hui Zheng, Erwin Sigel, Roland Baur, Hong Ren, Zhi Wang Li, J Tze-Fei Wong, and Hong Xue. 2002. "Anxiolytic Effect of Wogonin, a Benzodiazepine Receptor Ligand Isolated From Scutellaria Baicalensis Georgi.." *Biochemical Pharmacology* 64 (9): 1415–24.

Imai, Hissei, Aran Tajika, Peiyao Chen, Alessandro Pompoli, Giuseppe Guaiana, Mariasole Castellazzi, Irene Bighelli, *et al.* 2014. "Azapirones Versus Placebo for Panic Disorder in Adults.." *Cochrane Database of Systematic Reviews (Online)* 9: CD010828–28. doi:10.1002/14651858.CD010828.pub2.

Imanaka, A, S Morinobu, S Toki, S Yamamoto, A Matsuki, T Kozuru, and S Yamawaki. 2008. "Neonatal Tactile Stimulation Reverses the Effect of Neonatal Isolation on Open-Field and Anxiety-Like Behavior, and Pain Sensitivity in Male and Female Adult Sprague-Dawley Rats.." *Behavioural Brain Research* 186 (1): 91–97. doi:10.1016/j.bbr.2007.07.039.

Imanaka, Akihiro, Shigeru Morinobu, Shigeru Toki, and Shigeto Yamawaki. 2006. "Importance of Early Environment in the Development of Post-Traumatic Stress Disorder-Like Behaviors.." *Behavioural Brain Research* 173 (1): 129–37. doi:10.1016/j.bbr.2006.06.012.

Ishaq, Humera. 2014. "Anxiolytic Effect of Herbal Medicine, Khamira Gaozaban Ambri Jadwar Ood Salib Wala (KGJ) in Experimental Rat Models.." *Pakistan Journal of Pharmaceutical Sciences* 27 (2): 289–94.

Jain, Apar, Anna Dvorkin, Ehud Fonio, Ilan Golani, and Cornelius T Gross. 2012. "Validation of the Dimensionality Emergence Assay for the Measurement of Innate Anxiety in Laboratory Mice.." *European Neuropsychopharmacology : the Journal of the European College of Neuropsychopharmacology* 22 (2): 153–63. doi:10.1016/j.euroneuro.2011.07.001.

Jain, N S, K Hirani, and C T Chopde. 2005. "Reversal of Caffeine-Induced Anxiety by Neurosteroid 3-Alpha-Hydroxy-5-Alpha-Pregnane-20-One in Rats.." *Neuropharmacology* 48 (5): 627–38. doi:10.1016/j.neuropharm.2004.11.016.

Jastrzebska-Wiesek, Magdalena, Agata Siwek, Anna Partyka, Monika Kubacka, Szczepan Mogilski, Anna Wasik, Marcin Kolaczkowski, and Anna Wesolowska. 2014. "Pharmacological Evaluation of the Anxiolytic-Like Effects of EMD 386088, a Partial 5-HT6 Receptor Agonist, in the Rat Elevated Plus-Maze and Vogel Conflict Tests.." *Neuropharmacology* 85 (October): 253–62. doi:10.1016/j.neuropharm.2014.05.036.

Jászberényi, Miklós, Zsolt Bagosi, Balázs Thurzó, Imre Földesi, and Gyula Telegdy. 2007. "Endocrine and Behavioral Effects of Neuromedin S.." *Hormones and Behavior* 52 (5): 631–39. doi:10.1016/j.yhbeh.2007.08.002.

Jászberényi, Miklós, Zsolt Bagosi, Balázs Thurzó, Imre Földesi, Gyula Szabó, and Gyula Telegdy. 2009. "Endocrine, Behavioral and Autonomic Effects of Neuropeptide AF.." *Hormones and Behavior* 56 (1): 24–34. doi:10.1016/j.yhbeh.2009.02.006.

Jennings, Katie A, Merewyn K Loder, W John Sheward, Qi Pei, Robert M J Deacon, Matthew A Benson, Henry J Olverman, *et al.* 2006. "Increased Expression of the 5-HT Transporter Confers a Low-Anxiety Phenotype Linked to Decreased 5-HT Transmission.." *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience* 26 (35): 8955–64. doi:10.1523/JNEUROSCI.5356-05.2006.

Jessa, M, M Nazar, A Bidzinski, and A Plaznik. 1996. "The Effects of Repeated Administration of Diazepam, MK-801 and CGP 37849 on Rat Behavior in Two Models of Anxiety.." *European Neuropsychopharmacology* 6 (1): 55–61.

Jones, G H, C Schneider, H H Schneider, J Seidler, B J Cole, and D N Stephens. 1994. "Comparison of Several Benzodiazepine Receptor Ligands in Two Models of Anxiolytic

Activity in the Mouse: an Analysis Based on Fractional Receptor Occupancies.." *Psychopharmacology* 114 (2): 191–99.

Joshi, Jagdish C, Arunabha Ray, and Kavita Gulati. 2014. "Differential Modulatory Effects of Morphine on Acute and Chronic Stress Induced Neurobehavioral and Cellular Markers in Rats.." *European Journal of Pharmacology* 729 (April): 17–21. doi:10.1016/j.ejphar.2014.01.058.

Kalouda, Triantafyllia, and Nikolaos Pitsikas. 2015. "The Nitric Oxide Donor Molsidomine Induces Anxiolytic-Like Behaviour in Two Different Rat Models of Anxiety.." *Pharmacology Biochemistry and Behavior* 138 (November): 111–16. doi:10.1016/j.pbb.2015.09.004.

Kalueff, A V, M A Fox, P S Gallagher, and D L Murphy. 2007. "Hypolocomotion, Anxiety and Serotonin Syndrome-Like Behavior Contribute to the Complex Phenotype of Serotonin Transporter Knockout Mice.." *Genes, Brain, and Behavior* 6 (4): 389–400. doi:10.1111/j.1601-183X.2006.00270.x.

Kalueff, Allan V, Catherine L Jensen, and Dennis L Murphy. 2007. "Locomotory Patterns, Spatiotemporal Organization of Exploration and Spatial Memory in Serotonin Transporter Knockout Mice.." *Brain Research* 1169 (September): 87–97. doi:10.1016/j.brainres.2007.07.009.

Karakas, Alper, Hamit Coskun, Aliye Kaya, Aysegul Kucuk, and Bulent Gunduz. 2011. "The Effects of the Intraamygdalar Melatonin Injections on the Anxiety Like Behavior and the Spatial Memory Performance in Male Wistar Rats.." *Behavioural Brain Research* 222 (1): 141–50. doi:10.1016/j.bbr.2011.03.029.

Karim, Nasiara, Navnath Gavande, Petrine Wellendorph, Graham A R Johnston, Jane R Hanrahan, and Mary Chebib. 2011. "3-Hydroxy-2'-Methoxy-6-Methylflavone: a Potent Anxiolytic with a Unique Selectivity Profile at GABA(a) Receptor Subtypes.." *Biochemical Pharmacology* 82 (12): 1971–83. doi:10.1016/j.bcp.2011.09.002.

Kebebew, Zerihun, and Workineh Shibeshi. 2013. "Evaluation of Anxiolytic and Sedative Effects of 80% Ethanolic Carica Papaya L. (Caricaceae) Pulp Extract in Mice.." *Journal of Ethnopharmacology* 150 (2): 665–71. doi:10.1016/j.jep.2013.09.023.

Kirsch, Irving, Brett J Deacon, Tania B Huedo-Medina, Alan Scoboria, Thomas J Moore, and Blair T Johnson. 2008. "Initial Severity and Antidepressant Benefits: a Meta-Analysis of Data Submitted to the Food and Drug Administration." *PLoS Medicine* 5 (2): e45. doi:10.1371/journal.pmed.0050045.

Klemenhagen, Kristen C, Joshua A Gordon, Denis J David, René Hen, and Cornelius T Gross. 2006. "Increased Fear Response to Contextual Cues in Mice Lacking the 5-HT1A Receptor.." *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 31 (1): 101–11. doi:10.1038/sj.npp.1300774.

Klodzinska, A, E Tatarczynska, K Stachowicz, and E Chojnacka-Wojcik. 2004. "The Anxiolytic-Like Activity of AIDA (1-Aminoindan-1,5-Dicarboxylic Acid), an mGLu 1 Receptor Antagonist.." *Journal of Physiology and Pharmacology : an Official Journal of the Polish Physiological Society* 55 (1 Pt 1): 113–26.

Klodzinska, Aleksandra, Ewa Tatarczynska, Ewa Chojnacka-Wojcik, Gabriel Nowak, Nicholas D P Cosford, and Andrzej Pilc. 2004. "Anxiolytic-Like Effects of MTEP, a Potent and Selective mGlu5 Receptor Agonist Does Not Involve GABA(a) Signaling.." *Neuropharmacology* 47 (3): 342–50.

Knuth, Emily D, and Anne M Etgen. 2007. "Long-Term Behavioral Consequences of Brief, Repeated Neonatal Isolation.." *Brain Research* 1128 (1): 139–47. doi:10.1016/j.brainres.2006.10.054.

Koike, Hiroyuki, Daisuke Ibi, Hiroyuki Mizoguchi, Taku Nagai, Atsumi Nitta, Kazuhiro Takuma, Toshitaka Nabeshima, Yukio Yoneda, and Kiyofumi Yamada. 2009.

"Behavioral Abnormality and Pharmacologic Response in Social Isolation-Reared Mice.." *Behavioural Brain Research* 202 (1): 114–21. doi:10.1016/j.bbr.2009.03.028.

Kokare, Dadasaheb M, Manoj P Dandekar, Praful S Singru, Girdhari Lal Gupta, and Nishikant K Subhedar. 2010. "Involvement of Alpha-MSH in the Social Isolation Induced Anxiety- and Depression-Like Behaviors in Rat.." *Neuropharmacology* 58 (7): 1009–18. doi:10.1016/j.neuropharm.2010.01.006.

Kong, Wei Xi, Si Wei Chen, Yu Lei Li, Yi Jing Zhang, Rui Wang, Li Min, and Xiaojuan Mi. 2006. "Effects of Taurine on Rat Behaviors in Three Anxiety Models.." *Pharmacology Biochemistry and Behavior* 83 (2): 271–76. doi:10.1016/j.pbb.2006.02.007.

Kormos, Viktória, and Balázs Gaszner. 2013. "Role of Neuropeptides in Anxiety, Stress, and Depression: From Animals to Humans.." *Neuropeptides* 47 (6): 401–19. doi:10.1016/j.npep.2013.10.014.

Krishnan, Vaishnav, Ami Graham, Michelle S Mazei-Robison, Diane C Lagace, Kyoung-Shim Kim, Shari Birnbaum, Amelia J Eisch, *et al.* 2008. "Calcium-Sensitive Adenylyl Cyclases in Depression and Anxiety: Behavioral and Biochemical Consequences of Isoform Targeting." *Biological Psychiatry* 64 (4): 336–43. doi:10.1016/j.biopsych.2008.03.026.

Kumar, Dinesh, and Zulfiqar Ali Bhat. 2014. "Apigenin 7-Glucoside From Stachys Tibetica Vatke and Its Anxiolytic Effect in Rats.." *Phytomedicine : International Journal of Phytotherapy and Phytopharmacology* 21 (7): 1010–14. doi:10.1016/j.phymed.2013.12.001.

Kurhe, Yeshwant Vijay, Mahesh Radhakrishnan, Devadoss Thangaraj, and Deepali Gupta. 2014. "Anti-Anxiety Effect of a Novel 5-HT(3) Receptor Antagonist N-(Benzo[D]Thiazol-2-Yl)-3-Ethoxyquinoxalin-2-Carboxamide (6k) Using Battery Tests for Anxiety in Mice.." *Indian Journal of Pharmacology* 46 (1): 100–104.

Kuribara, H, E Kishi, M Kimura, S T Weintraub, and Y Maruyama. 2000. "Comparative Assessment of the Anxiolytic-Like Activities of Honokiol and Derivatives.." *Pharmacology Biochemistry and Behavior* 67 (3): 597–601.

Kusserow, Heike, Benjamin Davies, Heide Hörtnagl, Ingo Voigt, Thomas Stroh, Bettina Bert, Dong Rui Deng, Heidrun Fink, Rüdiger W Veh, and Franz Theuring. 2004. "Reduced Anxiety-Related Behaviour in Transgenic Mice Overexpressing Serotonin 1A Receptors.." *Brain Research Molecular Brain Research* 129 (1-2): 104–16. doi:10.1016/j.molbrainres.2004.06.028.

la Pena, de, June Bryan I, Hye Lim Lee, Seo Young Yoon, Gun Hee Kim, Yong Soo Lee, and Jae Hoon Cheong. 2013. "The Involvement of Magnoflorine in the Sedative and Anxiolytic Effects of Sinomeni Caulis Et Rhizoma in Mice.." *Journal of Natural Medicines* 67 (4): 814–21. doi:10.1007/s11418-013-0754-3.

LaBuda, C J, and P N Fuchs. 2001. "The Anxiolytic Effect of Acute Ethanol or Diazepam Exposure Is Unaltered in Mu-Opioid Receptor Knockout Mice.." *Brain Research Bulletin* 55 (6): 755–60.

Langen, Barbara, Ute Egerland, Katrin Bernoster, Rita Dost, Klaus Unverferth, and Chris Rundfeldt. 2005. "Characterization in Rats of the Anxiolytic Potential of ELB139 [1-(4-Chlorophenyl)-4-Piperidin-1-Yl-1,5-Dihydro-Imidazol-2-on], a New Agonist at the Benzodiazepine Binding Site of the GABAA Receptor.." *The Journal of Pharmacology and Experimental Therapeutics* 314 (2): 717–24. doi:10.1124/jpet.105.084681.

Lapiz, M D, Y Mateo, S Durkin, T Parker, and C A Marsden. 2001. "Effects of Central Noradrenaline Depletion by the Selective Neurotoxin DSP-4 on the Behaviour of the Isolated Rat in the Elevated Plus Maze and Water Maze.." *Psychopharmacology* 155 (3): 251–59.

Leggio, Gian Marco, Vincenzo Micale, Bernard Le Foll, Carmen Mazzola, Jose N Nobrega,

and Filippo Drago. 2011. “Dopamine D3 Receptor Knock-Out Mice Exhibit Increased Behavioral Sensitivity to the Anxiolytic Drug Diazepam..” *European Neuropsychopharmacology* 21 (4): 325–32. doi:10.1016/j.euroneuro.2010.05.006.

Leite-Almeida, Hugo, João José Cerqueira, Hong Wei, Nuno Ribeiro-Costa, Helena Anjos-Martins, Nuno Sousa, Antti Pertovaara, and Armando Almeida. 2012. “Differential Effects of Left/Right Neuropathy on Rats' Anxiety and Cognitive Behavior..” *Pain* 153 (11): 2218–25. doi:10.1016/j.pain.2012.07.007.

Lepicard, E M, C Joubert, I Hagneau, F Perez-Diaz, and G Chapouthier. 2000. “Differences in Anxiety-Related Behavior and Response to Diazepam in BALB/cByJ and C57BL/6J Strains of Mice..” *Pharmacology Biochemistry and Behavior* 67 (4): 739–48.

Leussis, Melanie P, and Susan L Andersen. 2008. “Is Adolescence a Sensitive Period for Depression? Behavioral and Neuroanatomical Findings From a Social Stress Model..” *Synapse (New York, N.Y.)* 62 (1): 22–30. doi:10.1002/syn.20462.

Li, Qian, Andrew Holmes, Li Ma, Louis D Van de Kar, Francisca Garcia, and Dennis L Murphy. 2004. “Medial Hypothalamic 5-Hydroxytryptamine (5-HT)1A Receptors Regulate Neuroendocrine Responses to Stress and Exploratory Locomotor Activity: Application of Recombinant Adenovirus Containing 5-HT1A Sequences..” *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience* 24 (48): 10868–77. doi:10.1523/JNEUROSCI.3223-04.2004.

Liebsch, G, R Landgraf, M Engelmann, P Lörscher, and F Holsboer. 1999. “Differential Behavioural Effects of Chronic Infusion of CRH 1 and CRH 2 Receptor Antisense Oligonucleotides Into the Rat Brain..” *Journal of Psychiatric Research* 33 (2): 153–63.

Liebsch, G, R Landgraf, R Gerstberger, J C Probst, C T Wotjak, M Engelmann, F Holsboer, and A Montkowski. 1995. “Chronic Infusion of a CRH1 Receptor Antisense Oligodeoxynucleotide Into the Central Nucleus of the Amygdala Reduced Anxiety-Related Behavior in Socially Defeated Rats..” *Regulatory Peptides* 59 (2): 229–39.

Line, Samantha J, Christopher Barkus, Clare Coyle, Katie A Jennings, Robert M Deacon, Klaus P Lesch, Trevor Sharp, and David M Bannerman. 2011. “Opposing Alterations in Anxiety and Species-Typical Behaviours in Serotonin Transporter Overexpressor and Knockout Mice..” *European Neuropsychopharmacology : the Journal of the European College of Neuropsychopharmacology* 21 (1): 108–16. doi:10.1016/j.euroneuro.2010.08.005.

Linge, Raquel, Angel Pazos, and Alvaro Diaz. 2013. “Social Isolation Differentially Affects Anxiety and Depressive-Like Responses of Bulbectomized Mice..” *Behavioural Brain Research* 245 (May): 1–6. doi:10.1016/j.bbr.2013.01.041.

Lira, Alena, Mingming Zhou, Nathalie Castanon, Mark S Ansorge, Joshua A Gordon, Jasmine H Francis, Maria Bradley-Moore, *et al.* 2003. “Altered Depression-Related Behaviors and Functional Changes in the Dorsal Raphe Nucleus of Serotonin Transporter-Deficient Mice..” *Biological Psychiatry* 54 (10): 960–71. http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6T4S-4B0KRCT-6&_user=126524&_coverDate=11%2F15%2F2003&_rdoc=1&_fmt=high&_orig=gateway&_origin=gateway&_sort=d&_docanchor=&view=c&_acct=C000010360&_version=1&_urlVersion=0&_userid=126524&md5=6b2461dc4bd1c99fe45dee4a7bc26540&searchtype=a.

Liu, Chen, Takashi Maejima, Steven C Wyler, Gemma Casadesus, Stefan Herlitze, and Evan S Deneris. 2010. “Pet-1 Is Required Across Different Stages of Life to Regulate Serotonergic Function..” *Nature Neuroscience* 13 (10): 1190–98. doi:10.1038/nn.2623.

Liu, Jie, Wei-Min Zhai, Yuan-Xiao Yang, Jin-Li Shi, Qian-Tong Liu, Guo-Lin Liu, Nan Fang, Jian Li, and Jian-You Guo. 2015. “GABA and 5-HT Systems Are Implicated in the Anxiolytic-Like Effect of Spinosin in Mice..” *Pharmacology Biochemistry and Behavior*

128 (January): 41–49. doi:10.1016/j.pbb.2014.11.003.

Liu, Jing, Jacob C Garza, Wei Li, and Xin-Yun Lu. 2011. “Melanocortin-4 Receptor in the Medial Amygdala Regulates Emotional Stress-Induced Anxiety-Like Behaviour, Anorexia and Corticosterone Secretion..” *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)* 16 (01): 105–20. doi:10.1017/S146114571100174X.

Liu, Xiao, Ruiyong Wu, Fadao Tai, Leige Ma, Bin Wei, Xiangping Yang, Xia Zhang, and Rui Jia. 2013. “Effects of Group Housing on Stress Induced Emotional and Neuroendocrine Alterations..” *Brain Research* 1502 (March): 71–80. doi:10.1016/j.brainres.2013.01.044.

Liu, Yan, Liu Yang, Jin Yu, and Yu-Qiu Zhang. 2015. “Persistent, Comorbid Pain and Anxiety Can Be Uncoupled in a Mouse Model.” *Physiology & Behavior* 151 (October): 55–63. doi:10.1016/j.physbeh.2015.07.004.

Locchi, Federica, Rossella Dall'olio, Ottavio Gandolfi, and Roberto Rimondini. 2008. “Olanzapine Counteracts Stress-Induced Anxiety-Like Behavior in Rats..” *Neuroscience Letters* 438 (2): 146–49. doi:10.1016/j.neulet.2008.04.017.

Lolli, Luiz F, Claudia M Sato, Cassia V Romanini, Larissa De Biaggi Villas-Boas, Cid A Moraes Santos, and Rubia M W de Oliveira. 2007. “Possible Involvement of GABA a-Benzodiazepine Receptor in the Anxiolytic-Like Effect Induced by Passiflora Actinia Extracts in Mice..” *Journal of Ethnopharmacology* 111 (2): 308–14. doi:10.1016/j.jep.2006.11.021.

Lukkes, Jodi L, Maxim V Mokin, Jamie L Scholl, and Gina L Forster. 2009. “Adult Rats Exposed to Early-Life Social Isolation Exhibit Increased Anxiety and Conditioned Fear Behavior, and Altered Hormonal Stress Responses..” *Hormones and Behavior* 55 (1): 248–56. doi:10.1016/j.yhbeh.2008.10.014.

Lunga, P, and J Herbert. 2004. “17Beta-Oestradiol Modulates Glucocorticoid, Neural and Behavioural Adaptations to Repeated Restraint Stress in Female Rats..” *Journal of Neuroendocrinology* 16 (9): 776–85. doi:10.1111/j.1365-2826.2004.01234.x.

Mahendra, Poonam, and Shradha Bisht. 2011. “Anti-Anxiety Activity of Coriandrum Sativum Assessed Using Different Experimental Anxiety Models..” *Indian Journal of Pharmacology* 43 (5): 574–77.

Majercsik, Eszter, József Haller, Csilla Leveleki, Johanna Baranyi, József Halász, and Robert John Rodgers. 2003. “The Effect of Social Factors on the Anxiolytic Efficacy of Buspirone in Male Rats, Male Mice, and Men..” *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 27 (8): 1187–99. doi:10.1016/j.pnpbp.2003.09.013.

Mansouri, Mohammad Taghi, Mohammad Soltani, Bahareh Naghizadeh, Yaghoub Farbood, Ahmad Mashak, and Alireza Sarkaki. 2014. “A Possible Mechanism for the Anxiolytic-Like Effect of Gallic Acid in the Rat Elevated Plus Maze..” *Pharmacology Biochemistry and Behavior* 117 (February): 40–46. doi:10.1016/j.pbb.2013.12.011.

Martinez, A L, F Dominguez, S Orozco, M Chavez, H Salgado, M González, and M E Gonzalez-Trujano. 2006. “Neuropharmacological Effects of an Ethanol Extract of the Magnolia Dealbata Zucc. Leaves in Mice..” *Journal of Ethnopharmacology* 106 (2): 250–55. doi:10.1016/j.jep.2006.01.003.

Matsuzawa-Yanagida, Kiyomi, Minoru Narita, Mayumi Nakajima, Naoko Kuzumaki, Keiichi Niikura, Hiroyuki Nozaki, Tomoe Takagi, *et al.* 2008. “Usefulness of Antidepressants for Improving the Neuropathic Pain-Like State and Pain-Induced Anxiety Through Actions at Different Brain Sites..” *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 33 (8): 1952–65. doi:10.1038/sj.npp.1301590.

McCool, Brian A, and Ann M Chappell. 2009. “Early Social Isolation in Male Long-Evans Rats Alters Both Appetitive and Consummatory Behaviors Expressed During Operant Ethanol Self-Administration..” *Alcoholism, Clinical and Experimental Research* 33 (2): 273–82. doi:10.1111/j.1530-0277.2008.00830.x.

Mechan, Annis O, Paula M Moran, MartinJ Elliott, Andrew J Young, Michael H Joseph, and RichardA Green. 2002. “A Comparison Between Dark Agouti and Sprague-Dawley Rats in Their Behaviour on the Elevated Plus-Maze, Open-Field Apparatus and Activity Meters, and Their Response to Diazepam..” *Psychopharmacology* 159 (2): 188–95. doi:10.1007/s002130100902.

Melo, Francisca Helvira Cavalcante, Edith Teles Venancio, Damiao Pergentino de Sousa, Marta Maria de Franca Fonteles, Silvania Maria Mendes de Vasconcelos, Glauce Socorro Barros Viana, and Francisca Clea Florenco de Sousa. 2010. “Anxiolytic-Like Effect of Carvacrol (5-Isopropyl-2-Methylphenol) in Mice: Involvement with GABAergic Transmission..” *Fundamental & Clinical Pharmacology* 24 (4): 437–43. doi:10.1111/j.1472-8206.2009.00788.x.

Mesfin, Miraf, Kaleab Asres, and Workineh Shibeshi. 2014. “Evaluation of Anxiolytic Activity of the Essential Oil of the Aerial Part of Foeniculum Vulgare Miller in Mice..” *BMC Complementary and Alternative Medicine* 14: 310. doi:10.1186/1472-6882-14-310.

Meyer, Laurence, Naoual Boujedaini, Christine Patte-Mensah, and Ayikoe G Mensah-Nyagan. 2013. “Pharmacological Effect of Gelsemine on Anxiety-Like Behavior in Rat..” *Behavioural Brain Research* 253 (September): 90–94. doi:10.1016/j.bbr.2013.07.010.

Mi, Xiao Juan, Si Wei Chen, Wen Juan Wang, Rui Wang, Yi Jing Zhang, Wei Jing Li, and Yu Lei Li. 2005. “Anxiolytic-Like Effect of Paeonol in Mice..” *Pharmacology Biochemistry and Behavior* 81 (3): 683–87. doi:10.1016/j.pbb.2005.04.016.

Micale, Vincenzo, Alessandra Tamburella, Gian Marco Leggio, Carmen Mazzola, Valentina Li Volsi, and Filippo Drago. 2008. “Behavioral Effects of Saredutant, a Tachykinin NK2 Receptor Antagonist, in Experimental Models of Mood Disorders Under Basal and Stress-Related Conditions..” *Pharmacology Biochemistry and Behavior* 90 (3): 463–69. doi:10.1016/j.pbb.2008.04.003.

Micale, Vincenzo, Luigia Cristino, Alessandra Tamburella, Stefania Petrosino, Gian Marco Leggio, Filippo Drago, and Vincenzo Di Marzo. 2009. “Anxiolytic Effects in Mice of a Dual Blocker of Fatty Acid Amide Hydrolase and Transient Receptor Potential Vanilloid Type-1 Channels..” *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 34 (3): 593–606. doi:10.1038/npp.2008.98.

Molander, Anna C, Adam Mar, Agnes Norbury, Sarah Steventon, Margarita Moreno, Daniele Caprioli, David E H Theobald, *et al.* 2011. “High Impulsivity Predicting Vulnerability to Cocaine Addiction in Rats: Some Relationship with Novelty Preference but Not Novelty Reactivity, Anxiety or Stress..” *Psychopharmacology* 215 (4): 721–31. doi:10.1007/s00213-011-2167-x.

Molina-Hernandez, M, N P Tellez-Alcantara, J Perez Garcia, J I Olivera Lopez, and M Teresa Jaramillo. 2004. “Anxiolytic-Like Actions of Leaves of Casimiroa Edulis (Rutaceae) in Male Wistar Rats..” *Journal of Ethnopharmacology* 93 (1): 93–98.

Mora, S, G Díaz-Véliz, H Lungenstrass, M Garcia-Gonzalez, T Coto-Morales, C Poletti, T C M De Lima, M Herrera-Ruiz, and J Tortoriello. 2005. “Central Nervous System Activity of the Hydroalcoholic Extract of Casimiroa Edulis in Rats and Mice..” *Journal of Ethnopharmacology* 97 (2): 191–97. doi:10.1016/j.jep.2004.10.028.

Moragrega, I, M C Carrasco, P Vicens, and R Redolat. 2003. “Spatial Learning in Male Mice with Different Levels of Aggressiveness: Effects of Housing Conditions and Nicotine Administration..” *Behavioural Brain Research* 147 (1-2): 1–8.

Moreira, Maria Rosilene Candido, Mirian Graciela da Silva Stiebbe Salvadori, Antonia

Amanda Cardoso de Almeida, Damiao Pergentino de Sousa, Joaquin Jordan, Prabodh Satyal, Rivelilson Mendes de Freitas, and Reinaldo Nobrega de Almeida. 2014. "Anxiolytic-Like Effects and Mechanism of (-)-Myrtenol: a Monoterpene Alcohol.." *Neuroscience Letters* 579 (September): 119–24. doi:10.1016/j.neulet.2014.07.007.

Moya, Pablo R, Meredith A Fox, Catherine L Jensen, Justin L LaPorte, Helen T French, Jens R Wendland, and Dennis L Murphy. 2011. "Altered 5-HT2C Receptor Agonist-Induced Responses and 5-HT2C Receptor RNA Editing in the Amygdala of Serotonin Transporter Knockout Mice.." *BMC Pharmacology* 11: 3. doi:10.1186/1471-2210-11-3.

Müller, Marianne B, Stephan Zimmermann, Inge Sillaber, Thomas P Hagemeyer, Jan M Deussing, Peter Timpl, Michael S D Kormann, *et al.* 2003. "Limbic Corticotropin-Releasing Hormone Receptor 1 Mediates Anxiety-Related Behavior and Hormonal Adaptation to Stress.." *Nature Neuroscience* 6 (10): 1100–1107. doi:10.1038/nn1123.

Nagaraja, Thandaga S, Riaz Mahmood, V Krishna, B S Thippeswamy, and V P Veerapur. 2012. "Evaluation of Anxiolytic Effect of Erythrina Mysorensis Gamb. in Mice.." *Indian Journal of Pharmacology* 44 (4): 489–92.

Nosek, Katarzyna, Kristen Dennis, Brian M Andrus, Nasim Ahmadiyeh, Amber E Baum, Leah C Solberg Woods, and Eva E Redei. 2008. "Context and Strain-Dependent Behavioral Response to Stress.." *Behavioral and Brain Functions : BBF* 4: 23. doi:10.1186/1744-9081-4-23.

Ochoa-Sanchez, Rafael, Quentin Rainer, Stefano Comai, Gilberto Spadoni, Annalida Bedini, Silvia Rivara, Franco Fraschini, Marco Mor, Giorgio Tarzia, and Gabriella Gobbi. 2012. "Anxiolytic Effects of the Melatonin MT(2) Receptor Partial Agonist UCM765: Comparison with Melatonin and Diazepam.." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 39 (2): 318–25. doi:10.1016/j.pnpbp.2012.07.003.

Ognibene, Elisa, Paolo Bovicelli, Walter Adriani, Luciano Saso, and Giovanni Laviola. 2008. "Behavioral Effects of 6-Bromoflavanone and 5-Methoxy-6,8-Dibromoflavanone as Anxiolytic Compounds.." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 32 (1): 128–34. doi:10.1016/j.pnpbp.2007.07.023.

Okuyama, S, S Chaki, R Yoshikawa, S Ogawa, Y Suzuki, T Okubo, A Nakazato, M Nagamine, and K Tomisawa. 1999. "Neuropharmacological Profile of Peripheral Benzodiazepine Receptor Agonists, DAA1097 and DAA1106.." *Life Sciences* 64 (16): 1455–64.

Olivier, J D A, M G C Van Der Hart, R P L Van Swelm, P J Dederen, J R Homberg, T Cremers, P M T Deen, E Cuppen, A R Cools, and B A Ellenbroek. 2008. "A Study in Male and Female 5-HT Transporter Knockout Rats: an Animal Model for Anxiety and Depression Disorders.." *Neuroscience* 152 (3): 573–84. doi:10.1016/j.neuroscience.2007.12.032.

Onusic, G M, R L Nogueira, A M S Pereira, and M B Viana. 2002. "Effect of Acute Treatment with a Water-Alcohol Extract of Erythrina Mulungu on Anxiety-Related Responses in Rats.." *Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Médicas E Biológicas / Sociedade Brasileira De Biofísica [Et Al]* 35 (4): 473–77.

Ouagazzal, A-M, J-L Moreau, M Pauly-Evers, and F Jenck. 2003. "Impact of Environmental Housing Conditions on the Emotional Responses of Mice Deficient for Nociceptin/Orphanin FQ Peptide Precursor Gene.." *Behavioural Brain Research* 144 (1-2): 111–17.

Owens, M J, and C B Nemeroff. 1991. "Physiology and Pharmacology of Corticotropin-Releasing Factor.." *Pharmacological Reviews* 43 (4): 425–73.

Paez-Pereda, Marcelo, Felix Hausch, and Florian Holsboer. 2011. "Corticotropin Releasing Factor Receptor Antagonists for Major Depressive Disorder.." *Expert Opinion on*

Investigational Drugs 20 (4): 519–35. doi:10.1517/13543784.2011.565330.

Pain, L, P Oberling, A Launoy, and G Di Scala. 1999. "Effect of Nonsedative Doses of Propofol on an Innate Anxiogenic Situation in Rats.." *Anesthesiology* 90 (1): 191–96.

Paine, T A, S L Jackman, and M C Olmstead. 2002. "Cocaine-Induced Anxiety: Alleviation by Diazepam, but Not Buspirone, Dimenhydrinate or Diphenhydramine.." *Behavioural Pharmacology* 13 (7): 511–23.

Pang, Raina D, Zhuo Wang, Lauren P Klosinski, Yumei Guo, David H Herman, Tansu Celikel, Hong-Wei Dong, and Daniel P Holschneider. 2011. "Mapping Functional Brain Activation Using [14C]-Iodoantipyrine in Male Serotonin Transporter Knockout Mice.." *PLoS ONE* 6 (8): e23869. doi:10.1371/journal.pone.0023869.

Parent, Alexandre J, Nicolas Beaudet, Hélène Beaudry, Jenny Bergeron, Patrick Bérubé, Guy Drolet, Philippe Sarret, and Louis Gendron. 2012. "Increased Anxiety-Like Behaviors in Rats Experiencing Chronic Inflammatory Pain.." *Behavioural Brain Research* 229 (1): 160–67. doi:10.1016/j.bbr.2012.01.001.

Parks, C L, P S Robinson, E Sibille, T Shenk, and M Toth. 1998. "Increased Anxiety of Mice Lacking the serotonin1A Receptor.." *Proceedings of the National Academy of Sciences of the United States of America* 95 (18): 10734–39.

Pellow, S, P Chopin, S E File, and M Briley. 1985. "Validation of Open:Closed Arm Entries in an Elevated Plus-Maze as a Measure of Anxiety in the Rat.." *Journal of Neuroscience Methods* 14 (3): 149–67.

Peng, Wen-Huang, Chi-Rei Wu, Chia-Sheng Chen, Chung-Fung Chen, Zong-Chung Leu, and Ming-Tsuen Hsieh. 2004. "Anxiolytic Effect of Berberine on Exploratory Activity of the Mouse in Two Experimental Anxiety Models: Interaction with Drugs Acting at 5-HT Receptors.." *Life Sciences* 75 (20): 2451–62.

Perez-Caballero, Laura, Sonia Torres-Sanchez, Lidia Bravo, Juan Antonio Mico, and Esther Berrocoso. 2014. "Fluoxetine: a Case History of Its Discovery and Preclinical Development.." *Expert Opinion on Drug Discovery* 9 (5): 567–78. doi:10.1517/17460441.2014.907790.

Pires, Lucio Fernandes, Luciana Muratori Costa, Oskar Almeida Silva, Antonia Amanda Cardoso de Almeida, Gilberto Santos Cerqueira, Damiao Pergentino de Sousa, and Rivelilson Mendes de Freitas. 2013. "Anxiolytic-Like Effects of Carvacryl Acetate, a Derivative of Carvacrol, in Mice.." *Pharmacology Biochemistry and Behavior* 112 (November): 42–48. doi:10.1016/j.pbb.2013.09.001.

Pisu, Maria Giuseppina, Anna Garau, Pierluigi Olla, Francesca Biggio, Cinzia Utzeri, Riccardo Dore, and Mariangela Serra. 2013. "Altered Stress Responsiveness and Hypothalamic-Pituitary-Adrenal Axis Function in Male Rat Offspring of Socially Isolated Parents.." *J Neurochem* 126 (4): 493–502. doi:10.1111/jnc.12273.

Pisu, Maria Giuseppina, Maria Cristina Mostallino, Riccardo Dore, Elisabetta Maciocco, Pietro Paolo Secci, and Mariangela Serra. 2011. "Effects of Voluntary Ethanol Consumption on Emotional State and Stress Responsiveness in Socially Isolated Rats.." *European Neuropsychopharmacology* 21 (5): 414–25. doi:10.1016/j.euroneuro.2010.07.006.

Piszczek, Lukasz, Kevin Schlax, Anna Wyrzykowska, Agnieszka Piszczek, Enrica Audero, and Cornelius Thilo Gross. 2013. "Serotonin 1A Auto-Receptors Are Not Sufficient to Modulate Anxiety in Mice.." *The European Journal of Neuroscience* 38 (4): 2621–27. doi:10.1111/ejn.12260.

Plaznik, A, W Palejko, M Nazar, and M Jessa. 1994. "Effects of Antagonists at the NMDA Receptor Complex in Two Models of Anxiety.." *European Neuropsychopharmacology* 4 (4): 503–12.

Ponten, Emma, Anders Fredriksson, Torsten Gordh, Per Eriksson, and Henrik Viberg. 2011.

"Neonatal Exposure to Propofol Affects BDNF but Not CaMKII, GAP-43, Synaptophysin and Tau in the Neonatal Brain and Causes an Altered Behavioural Response to Diazepam in the Adult Mouse Brain.." *Behavioural Brain Research* 223 (1): 75–80. doi:10.1016/j.bbr.2011.04.019.

Popik, Piotr, Emmanuel Kostakis, Martyna Krawczyk, Gabriel Nowak, Bernadeta Szewczyk, Philip Krieter, Zhengming Chen, *et al.* 2006. "The Anxioselective Agent 7-(2-Chloropyridin-4-Yl)Pyrazolo-[1,5-a]-Pyrimidin-3-Yl](Pyridin-2-Yl)Methanone (DOV 51892) Is More Efficacious Than Diazepam at Enhancing GABA-Gated Currents at Alpha1 Subunit-Containing GABAA Receptors.." *The Journal of Pharmacology and Experimental Therapeutics* 319 (3): 1244–52. doi:10.1124/jpet.106.107201.

Powell, Craig M, Susanne Schoch, Lisa Monteggia, Michel Barrot, Maria F Matos, Nicole Feldmann, Thomas C Südhof, and Eric J Nestler. 2004. "The Presynaptic Active Zone Protein RIM1alpha Is Critical for Normal Learning and Memory.." *Neuron* 42 (1): 143–53.

Pritchard, Laurel M, Tracey A Van Kempen, Heather Williams, and Betty Zimmerberg. 2008. "A Laboratory Exercise for a College-Level, Introductory Neuroscience Course Demonstrating Effects of Housing Environment on Anxiety and Psychostimulant Sensitivity.." *Journal of Undergraduate Neuroscience Education : JUNE : a Publication of FUN, Faculty for Undergraduate Neuroscience* 7 (1): A26–A32.

Prut, Laetitia, and Catherine Belzung. 2003. "The Open Field as a Paradigm to Measure the Effects of Drugs on Anxiety-Like Behaviors: a Review." *European Journal of Pharmacology* 463 (1-3): 3–33. doi:10.1016/S0014-2999(03)01272-X.

Quintino-dos-Santos, Jeyce Willig, Claudia Janaina Torres Muller, Cristie Setubal Bernabe, Caroline Azevedo Rosa, Sergio Tufik, and Luiz Carlos Schenberg. 2014. "Evidence That the Periaqueductal Gray Matter Mediates the Facilitation of Panic-Like Reactions in Neonatally-Isolated Adult Rats.." *PLoS ONE* 9 (3): e90726.

Radulovic, Niko S, Ana B Miltojevic, Pavle J Randjelovic, Nikola M Stojanovic, and Fabio Boylan. 2013. "Effects of Methyl and Isopropyl N-Methylanthranilates From Choisya Ternata Kunth (Rutaceae) on Experimental Anxiety and Depression in Mice.." *Phytotherapy Research : PTR* 27 (9): 1334–38. doi:10.1002/ptr.4877.

Rago, L, R A Kiivet, J Harro, and M Pold. 1988. "Behavioral Differences in an Elevated Plus-Maze: Correlation Between Anxiety and Decreased Number of GABA and Benzodiazepine Receptors in Mouse Cerebral Cortex.." *Naunyn-Schmiedeberg's Archives of Pharmacology* 337 (6): 675–78.

Ramanathan, M, A K Jaiswal, and S K Bhattacharya. 1998. "Differential Effects of Diazepam on Anxiety in Streptozotocin Induced Diabetic and Non-Diabetic Rats.." *Psychopharmacology* 135 (4): 361–67.

Ramboz, S, R Oosting, D A Amara, H F Kung, P Blier, M Mendelsohn, J J Mann, D Brunner, and R Hen. 1998. "Serotonin Receptor 1A Knockout: an Animal Model of Anxiety-Related Disorder.." *Proceedings of the National Academy of Sciences of the United States of America* 95 (24): 14476–81.

Raquibul Hasan, S M, M M Hossain, R Akter, M Jamila, E Hm Mazumder, and S Rahman. 2009. "Sedative and Anxiolytic Effects of Different Fractions of the Commelina Benghalensis Linn.." *Drug Discoveries & Therapeutics* 3 (5): 221–27.

Reis, Daniel G, América A Scopinho, Francisco S Guimarães, Fernando M A Corrêa, and Leonardo B M Resstel. 2011. "Behavioral and Autonomic Responses to Acute Restraint Stress Are Segregated Within the Lateral Septal Area of Rats.." *PLoS ONE* 6 (8): e23171. doi:10.1371/journal.pone.0023171.

Reis, Fernando M C V, Lucas Albrechet-Souza, Celso R Franci, and Marcus L Brandao. 2012. "Risk Assessment Behaviors Associated with Corticosterone Trigger the Defense Reaction to Social Isolation in Rats: Role of the Anterior Cingulate Cortex.." *Stress*

(Amsterdam, Netherlands) 15 (3): 318–28. doi:10.3109/10253890.2011.623740.

Rejon-Orantes, J C, D P Perdomo Suarez, A Rejon-Rodriguez, S Hernandez Hernandez, O E Garcia Lievano, D Lopez Rodriguez, and M Perez de la Mora. 2013. "Aqueous Root Extracts From Mimosa Albida Humb. & Bonpl. Ex Willd Display Antinociceptive Activity in Mice.." *Journal of Ethnopharmacology* 149 (2): 522–26. doi:10.1016/j.jep.2013.07.010.

Rex, Andre, Eve Morgenstern, and Heidrun Fink. 2002. "Anxiolytic-Like Effects of Kava-Kava in the Elevated Plus Maze Test--a Comparison with Diazepam.." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 26 (5): 855–60.

Rochford, J, S Beaulieu, I Rousse, J R Glowa, and N Barden. 1997. "Behavioral Reactivity to Aversive Stimuli in a Transgenic Mouse Model of Impaired Glucocorticoid (Type II) Receptor Function: Effects of Diazepam and FG-7142.." *Psychopharmacology* 132 (2): 145–52.

Rodgers, R J, and J C Cole. 1993. "Influence of Social Isolation, Gender, Strain, and Prior Novelty on Plus-Maze Behaviour in Mice.." *Physiology & Behavior* 54 (4): 729–36.

Rylkova, Daria, Hina P Shah, Elysia Small, and Adrie W Bruijnzeel. 2009. "Deficit in Brain Reward Function and Acute and Protracted Anxiety-Like Behavior After Discontinuation of a Chronic Alcohol Liquid Diet in Rats.." *Psychopharmacology* 203 (3): 629–40. doi:10.1007/s00213-008-1409-z.

Ryu, Vitaly, Sang Bae Yoo, Dong-Won Kang, Jong-Ho Lee, and Jeong Won Jahng. 2009. "Post-Weaning Isolation Promotes Food Intake and Body Weight Gain in Rats That Experienced Neonatal Maternal Separation.." *Brain Research* 1295 (October): 127–34. doi:10.1016/j.brainres.2009.08.006.

Saiyudthong, Somrudee, and Charles A Marsden. 2011. "Acute Effects of Bergamot Oil on Anxiety-Related Behaviour and Corticosterone Level in Rats.." *Phytotherapy Research : PTR* 25 (6): 858–62. doi:10.1002/ptr.3325.

Sakaue, Masaki, Yukio Ago, Chikako Sowa, Yutaka Koyama, Akemichi Baba, and Toshio Matsuda. 2003. "The 5-HT1A Receptor Agonist MKC-242 Increases the Exploratory Activity of Mice in the Elevated Plus-Maze.." *European Journal of Pharmacology* 458 (1-2): 141–44.

Samuels, Benjamin Adam, Indira Mendez-David, Charlène Faye, Sylvain André David, Kerri A Pierz, Alain M Gardier, René Hen, and Denis J David. 2014. "Serotonin 1A and Serotonin 4 Receptors: Essential Mediators of the Neurogenic and Behavioral Actions of Antidepressants.." *The Neuroscientist : a Review Journal Bringing Neurobiology, Neurology and Psychiatry*, December. doi:10.1177/1073858414561303.

Santos Rosa, Daiane, Silmara Aparecida Faggion, Amanda Salomao Gavin, Maicon Anderson de Souza, Helene Aparecida Fachim, Wagner Ferreira dos Santos, Ana Maria Soares Pereira, Alexandra Olimpio Siqueira Cunha, and Rene Oliveira Beleboni. 2012. "Erysothrine, an Alkaloid Extracted From Flowers of Erythrina Mulungu Mart. Ex Benth: Evaluating Its Anticonvulsant and Anxiolytic Potential.." *Epilepsy & Behavior : E&B* 23 (3): 205–12. doi:10.1016/j.yebeh.2012.01.003.

Santos, dos, Lucinéia, Telma G C S de Andrade, and Frederico G Graeff. 2010. "Social Separation and Diazepam Withdrawal Increase Anxiety in the Elevated Plus-Maze and Serotonin Turnover in the Median Raphe and Hippocampus.." *Journal of Psychopharmacology (Oxford, England)* 24 (5): 725–31. doi:10.1177/0269881109106954.

Satyan, K S, A K Jaiswal, S Ghosal, and S K Bhattacharya. 1998. "Anxiolytic Activity of Ginkgolic Acid Conjugates From Indian Ginkgo Biloba.." *Psychopharmacology* 136 (2): 148–52.

Schellinck, Heather M, Lianne Stanford, and Matthew Darrah. 2003. "Repetitive Acute Pain

in Infancy Increases Anxiety but Does Not Alter Spatial Learning Ability in Juvenile Mice.." *Behavioural Brain Research* 142 (1-2): 157–65. doi:10.1016/S0166-4328(02)00406-0.

Schipper, Pieter, Lourens J P Nonkes, Peter Karel, Amanda J Kiliaan, and Judith R Homberg. 2011. "Serotonin Transporter Genotype X Construction Stress Interaction in Rats.." *Behavioural Brain Research* 223 (1): 169–75. doi:10.1016/j.bbr.2011.04.037.

Schmitt, U, H Luddens, and C Hiemke. 2001. "Behavioral Analysis Indicates Benzodiazepine-Tolerance Mediated by the Benzodiazepine Binding-Site at the GABA(a)-Receptor.." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 25 (5): 1145–60.

Schmitt, U, H Luddens, and C Hiemke. 2002. "Anxiolytic-Like Effects of Acute and Chronic GABA Transporter Inhibition in Rats.." *Journal of Neural Transmission (Vienna, Austria : 1996)* 109 (5-6): 871–80. doi:10.1007/s007020200071.

Sena, Emily S, H Bart van der Worp, Philip M W Bath, David W Howells, and Malcolm R Macleod. 2010. "Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy.." *PLoS Biology* 8 (3): e1000344. doi:10.1371/journal.pbio.1000344.

Serra, M, M G Pisu, M Littera, G Papi, E Sanna, F Tuveri, L Usala, R H Purdy, and G Biggio. 2000. "Social Isolation-Induced Decreases in Both the Abundance of Neuroactive Steroids and GABA(a) Receptor Function in Rat Brain.." *J Neurochem* 75 (2): 732–40.

Shang, Lin, Tian-Le Xu, Fei Li, Jiansheng Su, and Wei-Guang Li. 2014. "Temporal Dynamics of Anxiety Phenotypes in a Dental Pulp Injury Model.." *Molecular Pain* 11 (1): 40–40. doi:10.1186/s12990-015-0040-3.

Sherif, F, and L Oreland. 1995. "Effect of the GABA-Transaminase Inhibitor Vigabatrin on Exploratory Behaviour in Socially Isolated Rats.." *Behavioural Brain Research* 72 (1-2): 135–40.

Sherif, F, J Harro, A el-Hwuegi, and L Oreland. 1994. "Anxiolytic-Like Effect of the GABA-Transaminase Inhibitor Vigabatrin (Gamma-Vinyl GABA) on Rat Exploratory Activity.." *Pharmacology Biochemistry and Behavior* 49 (4): 801–5.

Silva, Maria Izabel Gomes, Manuel Rufino de Aquino Neto, Paulo Florentino Teixeira Neto, Brinell Arcanjo Moura, Jeferson Falcao do Amaral, Damiao Pergentino de Sousa, Silvania Maria Mendes Vasconcelos, and Francisca Clea Florenco de Sousa. 2007. "Central Nervous System Activity of Acute Administration of Isopulegol in Mice.." *Pharmacology Biochemistry and Behavior* 88 (2): 141–47. doi:10.1016/j.pbb.2007.07.015.

Simon, P, R Dupuis, and J Costentin. 1994. "Thigmotaxis as an Index of Anxiety in Mice. Influence of Dopaminergic Transmissions.." *Behavioural Brain Research* 61 (1): 59–64.

Simpson, Joy, and John P Kelly. 2012. "The Effects of Isolated and Enriched Housing Conditions on Baseline and Drug-Induced Behavioural Responses in the Male Rat.." *Behavioural Brain Research* 234 (2): 175–83. doi:10.1016/j.bbr.2012.06.015.

Smith, G W, J M Aubry, F Dellu, A Contarino, L M Bilezikjian, L H Gold, R Chen, *et al.* 1998. "Corticotropin Releasing Factor Receptor 1-Deficient Mice Display Decreased Anxiety, Impaired Stress Response, and Aberrant Neuroendocrine Development." *Neuron* 20 (6): 1093–1102.

Sorra, Kumaraswamy, Chien-Shu Chen, Chi-Fen Chang, Srinivas Pusuluri, Khagga Mukkanti, Chi-Rei Wu, and Ta-Hsien Chuang. 2014. "Synthesis, Anticonvulsant, Sedative and Anxiolytic Activities of Novel Annulated Pyrrolo[1,4]Benzodiazepines.." *International Journal of Molecular Sciences* 15 (9): 16500–16510. doi:10.3390/ijms150916500.

Srinivasan, J, B Suresh, and M Ramanathan. 2003. "Differential Anxiolytic Effect of Enalapril

and Losartan in Normotensive and Renal Hypertensive Rats.." *Physiology & Behavior* 78 (4-5): 585–91.

Stankevicius, D, E C Rodrigues-Costa, J Camilo Florio, and J Palermo-Neto. 2008. "Neuroendocrine, Behavioral and Macrophage Activity Changes Induced by Picrotoxin Effects in Mice.." *Neuropharmacology* 54 (2): 300–308. doi:10.1016/j.neuropharm.2007.09.011.

Stefanski, R, W Palejko, W Kostowski, and A Plaznik. 1992. "The Comparison of Benzodiazepine Derivatives and Serotonergic Agonists and Antagonists in Two Animal Models of Anxiety.." *Neuropharmacology* 31 (12): 1251–58.

Steiner, Michel A, Hugues Lecourt, and Francois Jenck. 2012. "The Brain Orexin System and Almorexant in Fear-Conditioned Startle Reactions in the Rat.." *Psychopharmacology* 223 (4): 465–75. doi:10.1007/s00213-012-2736-7.

Stemmelin, Jeanne, Caroline Cohen, Jean-Paul Terranova, Matilde Lopez-Grancha, Philippe Pichat, Olivier Bergis, Michel Decobert, *et al.* 2008. "Stimulation of the Beta3-Adrenoceptor as a Novel Treatment Strategy for Anxiety and Depressive Disorders.." *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 33 (3): 574–87. doi:10.1038/sj.npp.1301424.

Sterne, Jonathan A C, Alex J Sutton, John P A Ioannidis, Norma Terrin, David R Jones, Joseph Lau, James Carpenter, *et al.* 2011. "Recommendations for Examining and Interpreting Funnel Plot Asymmetry in Meta-Analyses of Randomised Controlled Trials.." *BMJ (Clinical Research Ed.)* 343: d4002.

Storm, D R, C Hansel, B Hacker, A Parent, and D J Linden. 1998. "Impaired Cerebellar Long-Term Potentiation in Type I Adenylyl Cyclase Mutant Mice.." *Neuron* 20 (6): 1199–1210.

Sugiyama, Azusa, Akiyoshi Saitoh, Takashi Iwai, Kou Takahashi, Misa Yamada, Sachie Sasaki-Hamada, Jun-Ichiro Oka, Masatoshi Inagaki, and Mitsuhiko Yamada. 2012. "Riluzole Produces Distinct Anxiolytic-Like Effects in Rats Without the Adverse Effects Associated with Benzodiazepines.." *Neuropharmacology* 62 (8): 2489–98. doi:10.1016/j.neuropharm.2012.02.012.

Swami, Uma S, Aniruddha A Lande, Prachi M Ghadge, Prafulla P Adkar, and Shirishkumar D Ambavade. 2014. "Pharmacological Evaluation of Chlorophytum Borivilianum Sant. & Fern. for Anxiolytic Activity and Effect on Brain GABA Level." *Oriental Pharmacy and Experimental Medicine* 14 (2): 169–80. doi:10.1007/s13596-013-0145-z.

Taiwo, Adefunmilayo E, Franco B Leite, Greice M Lucena, Marilia Barros, Damaris Silveira, Monica V Silva, and Vania M Ferreira. 2012. "Anxiolytic and Antidepressant-Like Effects of Melissa Officinalis (Lemon Balm) Extract in Rats: Influence of Administration and Gender.." *Indian Journal of Pharmacology* 44 (2): 189–92. doi:10.4103/0253-7613.93846.

Tanaka, Machiko, Tadaaki Satou, and Kazuo Koike. 2013. "Anxiolytic-Like Effect of Shigyakusan Extract with Low Side Effects in Mice.." *Journal of Natural Medicines* 67 (4): 862–66. doi:10.1007/s11418-013-0746-3.

Tatarczynska, E, A Klodzinska, K Stachowicz, and E Chojnacka-Wojcik. 2004. "Effects of a Selective 5-HT1B Receptor Agonist and Antagonists in Animal Models of Anxiety and Depression.." *Behavioural Pharmacology* 15 (8): 523–34.

Thippeswamy, B S, Brijesh Mishra, V P Veerapur, and Gourav Gupta. 2011. "Anxiolytic Activity of Nymphaea Alba Linn. in Mice as Experimental Models of Anxiety.." *Indian Journal of Pharmacology* 43 (1): 50–55. doi:10.4103/0253-7613.75670.

Thompson, Trey, Laura Grabowski-Boase, and Lisa M Tarantino. 2015. "Prototypical Anxiolytics Do Not Reduce Anxiety-Like Behavior in the Open Field in C57BL/6J Mice.." *Pharmacology Biochemistry and Behavior* 133 (May): 7–17.

doi:10.1016/j.pbb.2015.03.011.

Thongsaard, W, C Deachapunya, S Pongsakorn, E A Boyd, G W Bennett, and C A Marsden. 1996. “Barakol: a Potential Anxiolytic Extracted From Cassia Siamea..” *Pharmacology Biochemistry and Behavior* 53 (3): 753–58.

Thorsell, Annika, Craig J Slawecki, Aram El Khoury, Aleksander A Mathe, and Cindy L Ehlers. 2006. “The Effects of Social Isolation on Neuropeptide Y Levels, Exploratory and Anxiety-Related Behaviors in Rats..” *Pharmacology Biochemistry and Behavior* 83 (1): 28–34. doi:10.1016/j.pbb.2005.12.005.

Tolardo, Rogerio, Lucas Zetterman, Daniel Rilo Bitencourtt, Ticiana Camila Mora, Fabio Lazzarotto de Oliveira, Maique Weber Biavatti, Solomon Kweku Sagoe Amoah, Cristiani Burger, and Marcia Maria de Souza. 2010. “Evaluation of Behavioral and Pharmacological Effects of Hedyosmum Brasiliense and Isolated Sesquiterpene Lactones in Rodents..” *Journal of Ethnopharmacology* 128 (1): 63–70. doi:10.1016/j.jep.2009.12.026.

Tone, Andrea. 2009. *The Age of Anxiety: a History of America's Turbulent Affair with Tranquilizers*. New York: Basic Books.

Trimble, N, A C Johnson, A Foster, and B Greenwood-van Meerveld. 2007. “Corticotropin-Releasing Factor Receptor 1-Deficient Mice Show Decreased Anxiety and Colonic Sensitivity..” *Neurogastroenterology and Motility : the Official Journal of the European Gastrointestinal Motility Society* 19 (9): 754–60. doi:10.1111/j.1365-2982.2007.00951.x.

van Praag, H M. 2003. “Can Stress Cause Depression?.” *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 28 (5): 891–907. doi:10.1016/j.pnpbp.2004.05.031.

Varty, Geoffrey B, Cynthia A Morgan, Mary E Cohen-Williams, Vicki L Coffin, and Galen J Carey. 2002. “The Gerbil Elevated Plus-Maze I: Behavioral Characterization and Pharmacological Validation..” *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology* 27 (3): 357–70. doi:10.1016/S0893-133X(02)00312-3.

Venancio, E T, N F M Rocha, E R V Rios, M L Feitosa, M I Linhares, F H C Melo, M S Matias, *et al.* 2011. “Anxiolytic-Like Effects of Standardized Extract of Justicia Pectoralis (SEJP) in Mice: Involvement of GABA/Benzodiazepine in Receptor..” *Phytotherapy Research : PTR* 25 (3): 444–50. doi:10.1002/ptr.3274.

Vesterinen, H M, E S Sena, K J Egan, T C Hirst, L Churolov, G L Currie, A Antonic, D W Howells, and M R Macleod. 2014. “Meta-Analysis of Data From Animal Studies: a Practical Guide..” *Journal of Neuroscience Methods* 221 (January): 92–102. doi:10.1016/j.jneumeth.2013.09.010.

Viechtbauer, Wolfgang. 2010. “Conducting Meta-Analyses in R with the Metafor Package.” *Journal of Statistical Software* 36 (3): 1–48. http://www.jstatsoft.org/v36/i03/paper.

Vinkers, Christiaan H, Ronald S Oosting, Meg J V van Bogaert, Berend Olivier, and Lucianne Groenink. 2010. “Early-Life Blockade of 5-HT(1A) Receptors Alters Adult Anxiety Behavior and Benzodiazepine Sensitivity..” *Biological Psychiatry* 67 (4): 309–16. doi:10.1016/j.biopsych.2009.08.013.

Voikar, V, A Polus, E Vasar, and H Rauvala. 2005. “Long-Term Individual Housing in C57BL/6J and DBA/2 Mice: Assessment of Behavioral Consequences..” *Genes, Brain, and Behavior* 4 (4): 240–52. doi:10.1111/j.1601-183X.2004.00106.x.

Volke, V, A Soosaar, S Koks, E Vasar, and P T Mannisto. 1998. “L-Arginine Abolishes the Anxiolytic-Like Effect of Diazepam in the Elevated Plus-Maze Test in Rats..” *European Journal of Pharmacology* 351 (3): 287–90.

Wada, T, and N Fukuda. 1991. “Effects of DN-2327, a New Anxiolytic, Diazepam and Buspirone on Exploratory Activity of the Rat in an Elevated Plus-Maze..”

Psychopharmacology 104 (4): 444–50.

Walf, Alicia A, and Cheryl A Frye. 2012. "Gestational or Acute Restraint in Adulthood Reduces Levels of 5alpha-Reduced Testosterone Metabolites in the Hippocampus and Produces Behavioral Inhibition of Adult Male Rats.." *Frontiers in Cellular Neuroscience* 6 (December): 1–11. doi:10.3389/fncel.2012.00040/abstract.

Wanasuntronwong, Aree, Mayuree H Tantisira, Boonyong Tantisira, and Hiroshi Watanabe. 2012. "Anxiolytic Effects of Standardized Extract of Centella Asiatica (ECa 233) After Chronic Immobilization Stress in Mice.." *Journal of Ethnopharmacology* 143 (2): 579–85. doi:10.1016/j.jep.2012.07.010.

Wang, Xiaohong, Guiyun Li, Peng Li, Linyuan Huang, Jianmei Huang, and Haifeng Zhai. 2015. "Anxiolytic Effects of Orcinol Glucoside and Orcinol Monohydrate in Mice.." *Pharmaceutical Biology* 53 (6): 876–81. doi:10.3109/13880209.2014.946060.

Wei, Xiu Yan, Jing Yu Yang, Ying Xu Dong, and Chun Fu Wu. 2007. "Anxiolytic-Like Effects of Oleamide in Group-Housed and Socially Isolated Mice.." *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 31 (6): 1189–95. doi:10.1016/j.pnpbp.2007.04.008.

Weninger, S C, A J Dunn, L J Muglia, P Dikkes, K A Miczek, A H Swiergiel, C W Berridge, and J A Majzoub. 1999. "Stress-Induced Behaviors Require the Corticotropin-Releasing Hormone (CRH) Receptor, but Not CRH.." *Proceedings of the National Academy of Sciences of the United States of America* 96 (14): 8283–88.

Wesolowska, Anna, and Agnieszka Nikiforuk. 2007. "Effects of the Brain-Penetrant and Selective 5-HT6 Receptor Antagonist SB-399885 in Animal Models of Anxiety and Depression.." *Neuropharmacology* 52 (5): 1274–83. doi:10.1016/j.neuropharm.2007.01.007.

Wikinski, S I, G B Acosta, M C Gravielle, C D Bonavita, V Bisagno, S Fiszer de Plazas, and M C Rubio. 2001. "Diazepam Fails to Potentiate GABA-Induced Chloride Uptake and to Produce Anxiolytic-Like Action in Aged Rats.." *Pharmacology Biochemistry and Behavior* 68 (4): 721–27.

Wolfman, C, H Viola, A Paladini, F Dajas, and J H Medina. 1994. "Possible Anxiolytic Effects of Chrysin, a Central Benzodiazepine Receptor Ligand Isolated From Passiflora Coerulea.." *Pharmacology Biochemistry and Behavior* 47 (1): 1–4.

Workman, Joanna L, Laura K Fonken, James Gusfa, Kathleen M Kassouf, and Randy J Nelson. 2011. "Post-Weaning Environmental Enrichment Alters Affective Responses and Interacts with Behavioral Testing to Alter nNOS Immunoreactivity.." *Pharmacology Biochemistry and Behavior* 100 (1): 25–32. doi:10.1016/j.pbb.2011.07.008.

Wright, R C, and A J Ingenito. 2001. "Prevention of Isolation-Induced Hypertension by Intrahippocampal Administration of a Nonpeptide Kappa-Opioid Receptor Agonist.." *Hippocampus* 11 (4): 445–51. doi:10.1002/hipo.1059.

Yadav, A V, L A Kawale, and V S Nade. 2008. "Effect of Morus Alba L. (Mulberry) Leaves on Anxiety in Mice.." *Indian Journal of Pharmacology* 40 (1): 32–36. doi:10.4103/0253-7613.40487.

Yamada, K, R Iida, Y Miyamoto, K Saito, K Sekikawa, M Seishima, and T Nabeshima. 2000. "Neurobehavioral Alterations in Mice with a Targeted Deletion of the Tumor Necrosis Factor-Alpha Gene: Implications for Emotional Behavior.." *Journal of Neuroimmunology* 111 (1-2): 131–38.

Yao, Yi, Min Jia, Jian-Guo Wu, Hong Zhang, Lian-Na Sun, Wan-Sheng Chen, and Khalid Rahman. 2010. "Anxiolytic and Sedative-Hypnotic Activities of Polygalasaponins From Polygala Tenuifolia in Mice.." *Pharmaceutical Biology* 48 (7): 801–7. doi:10.3109/13880200903280042.

Yasumatsu, H, Y Morimoto, Y Yamamoto, S Takehara, T Fukuda, T Nakao, and M

Setoguchi. 1994. “The Pharmacological Properties of Y-23684, a Benzodiazepine Receptor Partial Agonist..” *British Journal of Pharmacology* 111 (4): 1170–78.

Yildirim, Engin, Kevser Erol, and Emel Ulupinar. 2012. “Effects of Sertraline on Behavioral Alterations Caused by Environmental Enrichment and Social Isolation..” *Pharmacology Biochemistry and Behavior* 101 (2): 278–87. doi:10.1016/j.pbb.2011.12.017.

Yorgason, Jordan T, Rodrigo A Espana, Joanne K Konstantopoulos, Jeffrey L Weiner, and Sara R Jones. 2013. “Enduring Increases in Anxiety-Like Behavior and Rapid Nucleus Accumbens Dopamine Signaling in Socially Isolated Rats..” *The European Journal of Neuroscience* 37 (6): 1022–31. doi:10.1111/ejn.12113.

Zanoli, P, M Rivasi, C Baraldi, and M Baraldi. 2002. “Pharmacological Activity of Hyperforin Acetate in Rats..” *Behavioural Pharmacology* 13 (8): 645–51. doi:10.1097/01.fbp.0000047149.28986.2e.

Zhang, Li-Ming, Nan Zhao, Wen-Zhi Guo, Zeng-Liang Jin, Zhi-Kun Qiu, Hong-Xia Chen, Rui Xue, You-Zhi Zhang, Ri-Fang Yang, and Yun-Feng Li. 2014. “Antidepressant-Like and Anxiolytic-Like Effects of YL-IPA08, a Potent Ligand for the Translocator Protein (18 kDa)..” *Neuropharmacology* 81 (June): 116–25. doi:10.1016/j.neuropharm.2013.09.016.

Zhang, Yong, Xuyu Zu, Weishi Luo, Hongwei Yang, Guoxuan Luo, Mengxia Zhang, and Shengsong Tang. 2012. “Social Isolation Produces Anxiety-Like Behaviors and Changes PSD-95 Levels in the Forebrain..” *Neuroscience Letters* 514 (1): 27–30. doi:10.1016/j.neulet.2012.02.043.

Zhao, S, J Edwards, J Carroll, L Wiedholz, R A Millstein, C Jaing, D L Murphy, T H Lanthorn, and A Holmes. 2006. “Insertion Mutation at the C-Terminus of the Serotonin Transporter Disrupts Brain Serotonin Function and Emotion-Related Behaviors in Mice..” *Neuroscience* 140 (1): 321–34. doi:10.1016/j.neuroscience.2006.01.049.

Zheng, F, H Adelsberger, M R Muller, J M Fritschy, S Werner, and C Alzheimer. 2009. “Activin Tunes GABAergic Neurotransmission and Modulates Anxiety-Like Behavior..” *Molecular Psychiatry* 14 (3): 332–46. doi:10.1038/sj.mp.4002131.

FIGURES AND TABLES

Figure 1. Flow chart of the systematic literature review of 10 anxiotropic interventions. The literature was reviewed in a four-stage process, starting with searches of the Pubmed and EMBASE databases that yielded 1156 articles, followed by three screens of increasing detail, reviewing the article title, abstract, and full text for experimental design. A total of 298 articles were used in the meta-analysis. Further details are given in Table 1 and the Methods section.

Figure 2. Funnel plots of three meta-analyses with evidence for publication bias. Where at least ten experiments were available for meta-analysis, the effect sizes (Hedges' *g*) of the experiments are plotted against their respective standard errors. Points on each plot represent individual experiments. The triangle bounded by dotted lines indicates the area where 95% of studies are expected to fall, in the absence of both publication bias and study heterogeneity. Shown here are funnel plots for experiments on (A) diazepam, (B) social isolation, --and (C) Htt knockout.

Figure 3. Meta-analysis of diazepam on rodent anxiety related behavior. Meta-analysis of rodent diazepam effect sizes, shown as a forest plot of standardized effect sizes (Hedges' g). The meta-analysis is sub-grouped by animal species. Error bars indicate the 95% confidence intervals of standardized mean difference. The weighted average mean effect size of subgroups and all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes are given in the columns listed as N_C and N_T respectively.

Figure 4. Meta-analyses of serotonin receptor 1A interventions on rodent anxiety-related behaviors. Meta-analysis of effect sizes of serotonin-targeted interventions is shown as a forest plot of standardized effect sizes (Hedges' *g*). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N_C, N_T) and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD). Effects of: A. Serotonin receptor gene Htr1a knockout models. B. Htr1a overexpression.

Figure 5. Meta-analyses of serotonin transporter interventions on rodent anxiety-related behaviors.

Meta-analysis of effect sizes of serotonin-targeted interventions is shown as a forest plot of standardized effect sizes (Hedges' *g*). Error bars indicate the 95% confidence intervals of *g*. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N_C, N_T) and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD). Effects of: A. Serotonin transporter gene (*Htt*) knockout models B. *Htt* overexpression models.

Figure 6. Meta-analyses of experiments on the stress-anxiety relationship in rodents.

Meta-analysis of effect sizes of stress-anxiety interventions, shown as a forest plot of standardized effect sizes (Hedges' *g*). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N_C, N_T) and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD). Effects of: A. Acute pain. B. Restraint stress (immobilization). C. Social isolation.

Figure 7. Meta-analyses of the effects of stress signaling genes on anxiety-related behaviors.

Meta-analysis of effect sizes of stress signaling genes, shown as a forest plot of standardized effect sizes (Hedges' *g*). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N_C, N_T) and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD). Effects of: A. *Crh* gene knockout models. B. *Crhr1* gene knockout models.

Figure 8. Meta-analyses of interventions known to be unrelated to anxiety.

Meta-analysis of effect sizes of non-anxiety-related interventions, shown as a forest plot of standardized effect sizes (Hedges' *g*). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N_C, N_T) and the assay types of the studies are given; elevated plus

maze (EPM), open field (OF) and light-dark box (LD). Effects of: A. *Adcy1* gene knockout models. B. Synaptotagmin gene (*Syt1*) mutation models.

Figure 9. Summary effect sizes of all meta-analyses.

The weighted mean effect sizes of all 12 interventions are shown here. Each mean effect size is represented by the central vertices of a diamond; the outer vertices indicate the 95% confidence intervals. The horizontal axis is Hedges' *g,* the standard deviation change relative to control animals. Color indicates direction (green = anxiolytic, red = anxiogenic) and statistical significance (grey = statistically non-significant). The diamonds for the diazepam, social isolation, and Htt KO meta-analyses represent the summary effect sizes after trim-and-fill bias correction.

Table 1. Summary of systematic reviews of anxiety-related interventions in mouse and rat.

The PubMed and Embase query phrases used to identify articles that might contain data relevant to the interventions and assays of interest are detailed. Title, abstract and full-text searches were performed to identify articles meeting the selected criteria. Where there were fewer than fifteen articles meeting the selection criteria, all relevant data in all articles found were used for data extraction and meta-analysis. Where there were more articles, we took a random sample of fifteen papers and used only relevant data therein for meta-analysis.

Table 2. Results of Egger's linear regression test for funnel plot asymmetry across six meta-analyses

Where at least ten experiments were available for meta-analysis, Egger's linear regression test for funnel plot asymmetry was performed. For each meta-analysis, the number of studies included, the vertical intercept of the linear regression, the corresponding 95% confidence interval for the intercept, and the p-value of Egger's test are listed.

Table 3. Characteristics of included experiments.

Characteristics of experiments from included studies are listed with Pubmed ID, year of study, and figure panel. The assay type, assay duration, variable used in experiment, route of injection, drug dosage, treatment duration, species, strain and gender are also detailed. Assay duration and treatment duration are listed in minutes. Dosage is listed in mg per kg body weight of animal. Cells containing NA indicate that the information is not available for the underlying intervention.

Supporting Information Legends

Supporting Information 1. Spreadsheet containing extracted data (.csv file)

Supporting Information 2. Extracted meta-analytic data in R-compatible format (.RData file)

Supporting Information 3. R markdown code (.Rmd) used for meta-analysis and plotting

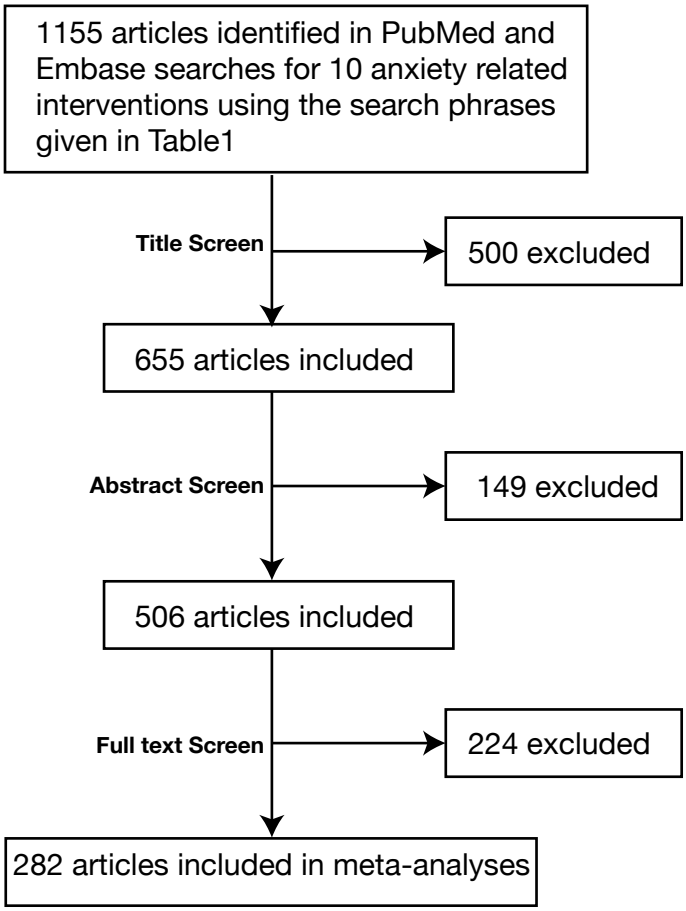


Figure 1. Flow chart of the systematic literature review of 10 anxiotropic interventions. The literature was reviewed in a four-stage process, starting with a PubMed search that yielded 1156 articles, followed by three screens of increasing detail, reviewing the article title, abstract, and full text for experimental design. A total of 297 articles were used in the meta-analysis. Further details are given in Table 1 and the Methods section.

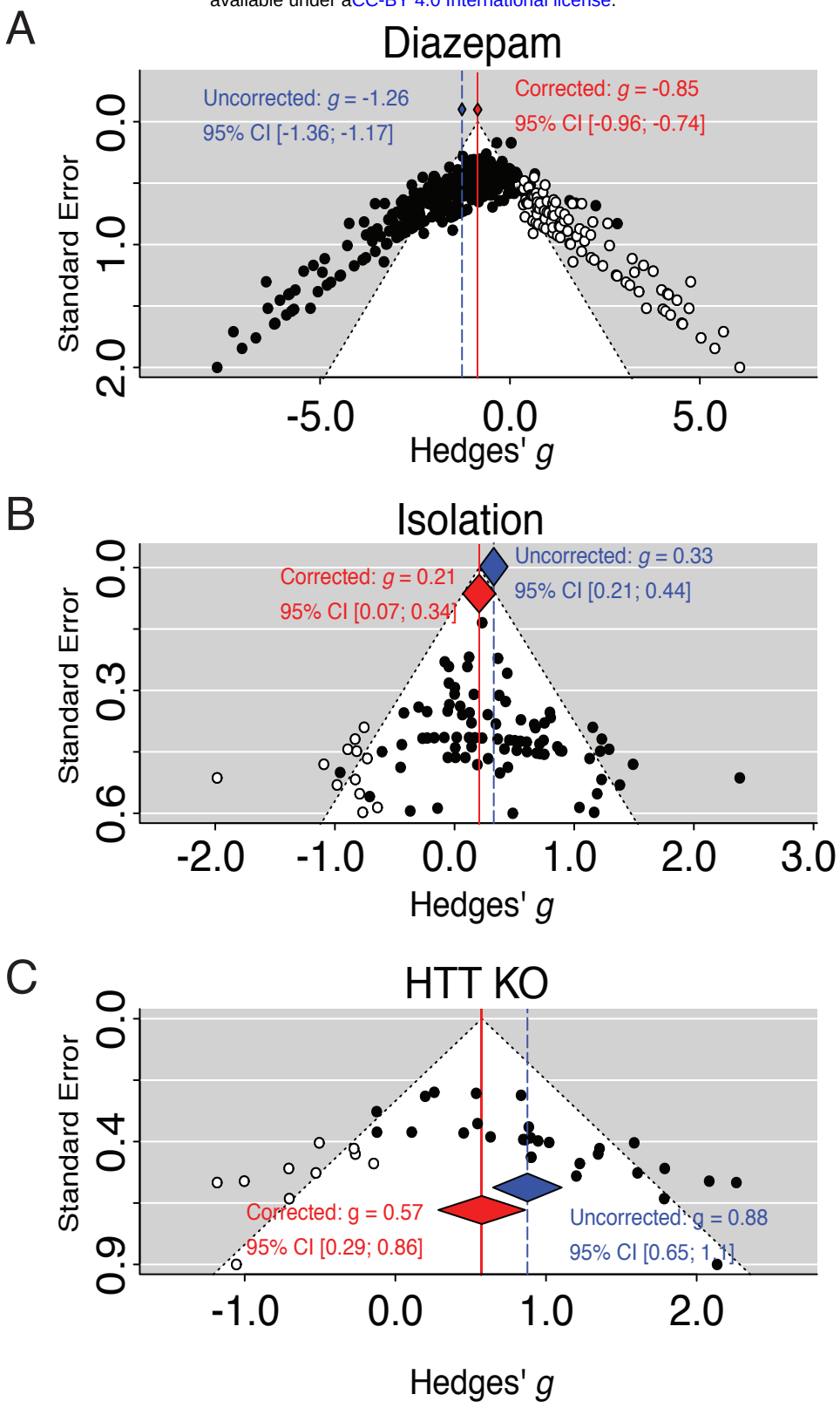
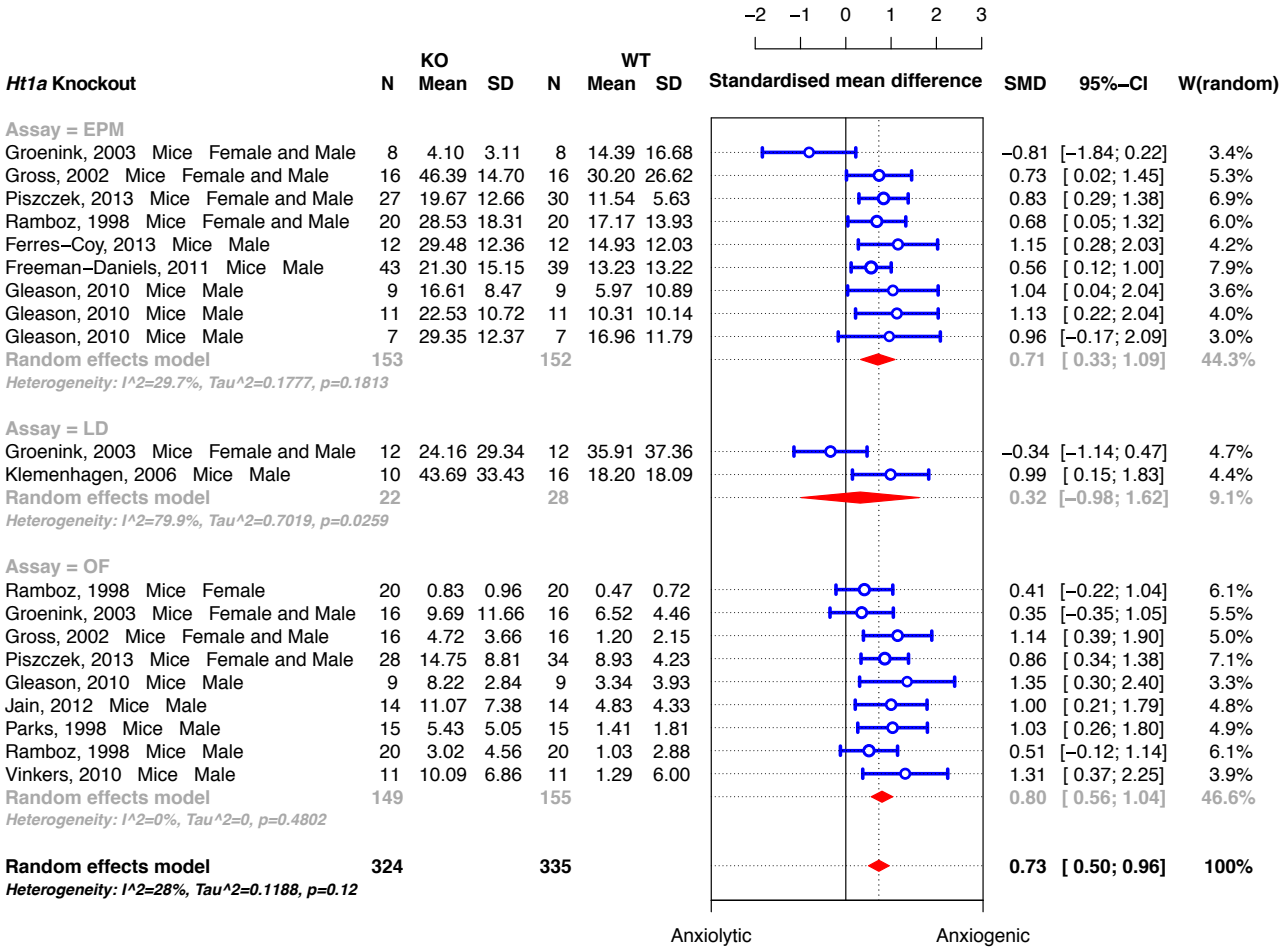


Figure 2. Funnel Plots for Three Meta-Analysis With Evidence of Publication Bias. Where at least ten experiments were available for meta-analysis, the effect sizes (Hedges' g) of the experiments are plotted against their respective standard errors. Points on each plot represent individual experiments. The triangle bounded by dotted lines indicates the area where 95% of studies are expected to fall, in the absence of both publication bias and study heterogeneity. Shown here are funnel plots for experiments on **(A)** diazepam, **(B)** social isolation, and **(C)** Htt knockout.

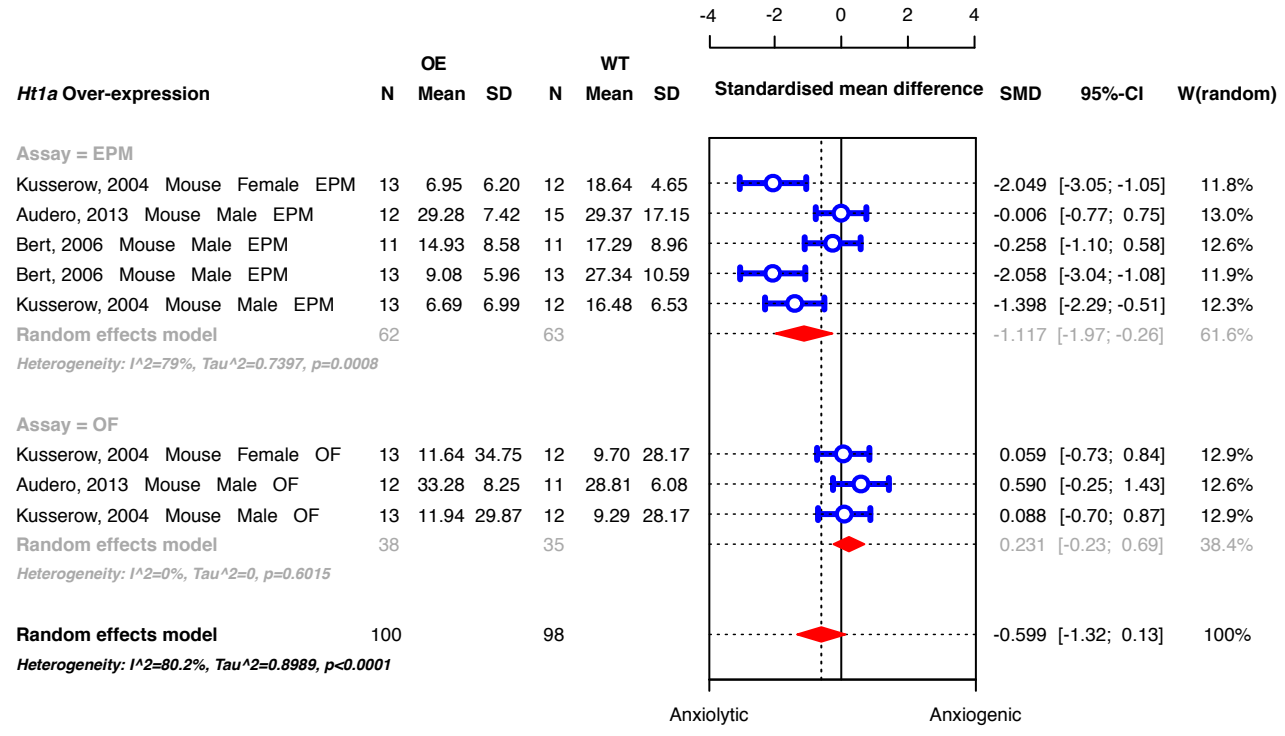
Figure 3. Meta-analysis of diazepam on rodent anxiety related behavior.
Meta-analysis of rodent diazepam effect sizes, shown as a forest plot of standardized effect sizes (Hedges' g). The meta-analysis is sub-grouped by animal species. Error bars indicate the 95% confidence intervals of standardized mean difference (SMD). The weighted average mean effect size of subgroups and all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes are given in the columns listed as N_C and N_T respectively.

A



Ht1a Knockout	KO N	KO Mean	KO SD	WT N	WT Mean	WT SD	SMD	95%−CI	W(random)
Assay = EPM									
Groenink, 2003 Mice Female and Male	8	4.10	3.11	8	14.39	16.68	−0.81	[−1.84; 0.22]	3.4%
Gross, 2002 Mice Female and Male	16	46.39	14.70	16	30.20	26.62	0.73	[0.02; 1.45]	5.3%
Piszczek, 2013 Mice Female and Male	27	19.67	12.66	30	11.54	5.63	0.83	[0.29; 1.38]	6.9%
Ramboz, 1998 Mice Female and Male	20	28.53	18.31	20	17.17	13.93	0.68	[0.05; 1.32]	6.0%
Ferres−Coy, 2013 Mice Male	12	29.48	12.36	12	14.93	12.03	1.15	[0.28; 2.03]	4.2%
Freeman−Daniels, 2011 Mice Male	43	21.30	15.15	39	13.23	13.22	0.56	[0.12; 1.00]	7.9%
Gleason, 2010 Mice Male	9	16.61	8.47	9	5.97	10.89	1.04	[0.04; 2.04]	3.6%
Gleason, 2010 Mice Male	11	22.53	10.72	11	10.31	10.14	1.13	[0.22; 2.04]	4.0%
Gleason, 2010 Mice Male	7	29.35	12.37	7	16.96	11.79	0.96	[−0.17; 2.09]	3.0%
Random effects model	153			152			0.71	[0.33; 1.09]	44.3%
Heterogeneity: I^2=29.7%, Tau^2=0.1777, p=0.1813									
Assay = LD									
Groenink, 2003 Mice Female and Male	12	24.16	29.34	12	35.91	37.36	−0.34	[−1.14; 0.47]	4.7%
Klemenhagen, 2006 Mice Male	10	43.69	33.43	16	18.20	18.09	0.99	[0.15; 1.83]	4.4%
Random effects model	22			28			0.32	[−0.98; 1.62]	9.1%
Heterogeneity: I^2=79.9%, Tau^2=0.7019, p=0.0259									
Assay = OF									
Ramboz, 1998 Mice Female	20	0.83	0.96	20	0.47	0.72	0.41	[−0.22; 1.04]	6.1%
Groenink, 2003 Mice Female and Male	16	9.69	11.66	16	6.52	4.46	0.35	[−0.35; 1.05]	5.5%
Gross, 2002 Mice Female and Male	16	4.72	3.66	16	1.20	2.15	1.14	[0.39; 1.90]	5.0%
Piszczek, 2013 Mice Female and Male	28	14.75	8.81	34	8.93	4.23	0.86	[0.34; 1.38]	7.1%
Gleason, 2010 Mice Male	9	8.22	2.84	9	3.34	3.93	1.35	[0.30; 2.40]	3.3%
Jain, 2012 Mice Male	14	11.07	7.38	14	4.83	4.33	1.00	[0.21; 1.79]	4.8%
Parks, 1998 Mice Male	15	5.43	5.05	15	1.41	1.81	1.03	[0.26; 1.80]	4.9%
Ramboz, 1998 Mice Male	20	3.02	4.56	20	1.03	2.88	0.51	[−0.12; 1.14]	6.1%
Vinkers, 2010 Mice Male	11	10.09	6.86	11	1.29	6.00	1.31	[0.37; 2.25]	3.9%
Random effects model	149			155			0.80	[0.56; 1.04]	46.6%
Heterogeneity: I^2=0%, Tau^2=0, p=0.4802									
Random effects model	**324**			**335**			**0.73**	**[0.50; 0.96]**	**100%**
Heterogeneity: I^2=28%, Tau^2=0.1188, p=0.12									

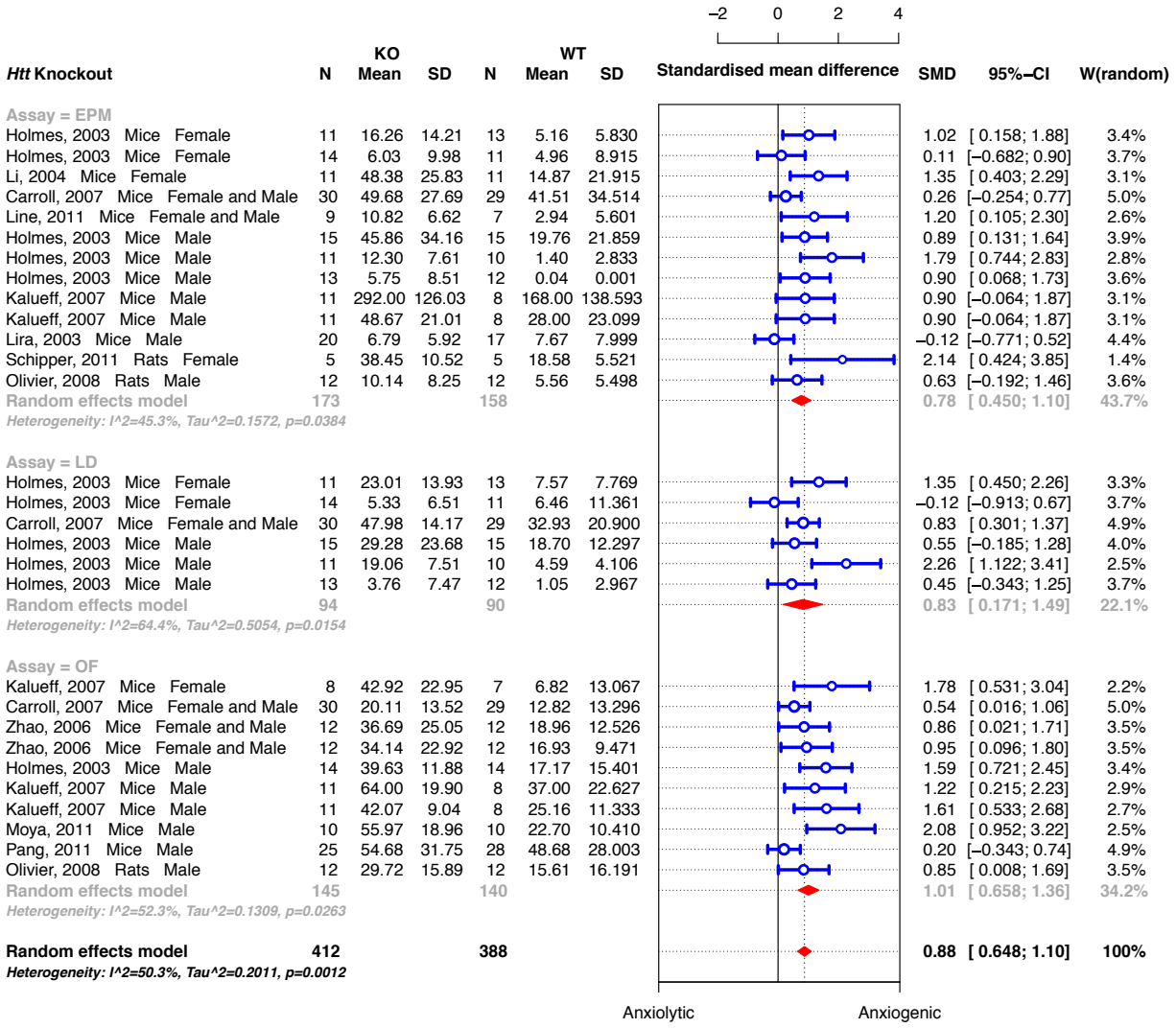
B



Ht1a Over-expression	OE N	OE Mean	OE SD	WT N	WT Mean	WT SD	SMD	95%-CI	W(random)
Assay = EPM									
Kusserow, 2004 Mouse Female EPM	13	6.95	6.20	12	18.64	4.65	-2.049	[-3.05; -1.05]	11.8%
Audero, 2013 Mouse Male EPM	12	29.28	7.42	15	29.37	17.15	-0.006	[-0.77; 0.75]	13.0%
Bert, 2006 Mouse Male EPM	11	14.93	8.58	11	17.29	8.96	-0.258	[-1.10; 0.58]	12.6%
Bert, 2006 Mouse Male EPM	13	9.08	5.96	13	27.34	10.59	-2.058	[-3.04; -1.08]	11.9%
Kusserow, 2004 Mouse Male EPM	13	6.69	6.99	12	16.48	6.53	-1.398	[-2.29; -0.51]	12.3%
Random effects model	62			63			-1.117	[-1.97; -0.26]	61.6%
Heterogeneity: I^2=79%, Tau^2=0.7397, p=0.0008									
Assay = OF									
Kusserow, 2004 Mouse Female OF	13	11.64	34.75	12	9.70	28.17	0.059	[-0.73; 0.84]	12.9%
Audero, 2013 Mouse Male OF	12	33.28	8.25	11	28.81	6.08	0.590	[-0.25; 1.43]	12.6%
Kusserow, 2004 Mouse Male OF	13	11.94	29.87	12	9.29	28.17	0.088	[-0.70; 0.87]	12.9%
Random effects model	38			35			0.231	[-0.23; 0.69]	38.4%
Heterogeneity: I^2=0%, Tau^2=0, p=0.6015									
Random effects model	100			98			-0.599	[-1.32; 0.13]	100%
Heterogeneity: I^2=80.2%, Tau^2=0.8989, p<0.0001									

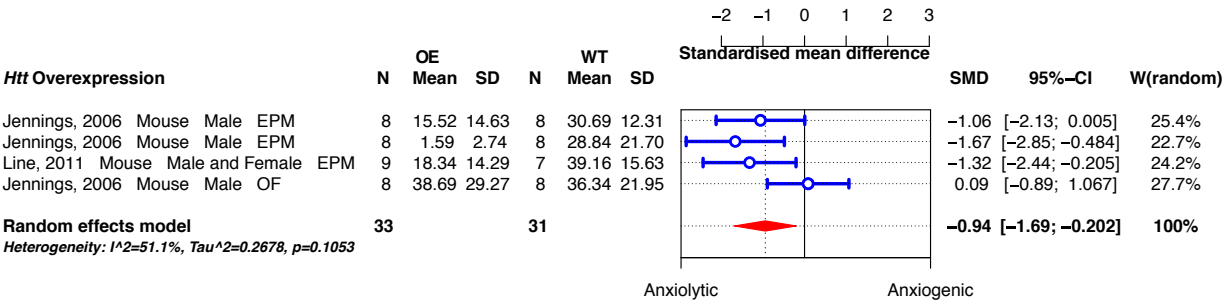
Figure 4. Meta-analyses of serotonin receptor interventions on rodent anxiety-related behaviors. Meta-analysis of effect sizes of serotonin-targeted interventions is shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N), the assay types of the studies, and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD). Effects of: **A.** Serotonin receptor gene (*Htr1a*) knockout models **B.** *Htr1a* overexpression models.

A



Htt Knockout	KO N	KO Mean	KO SD	WT N	WT Mean	WT SD	SMD	95%–CI	W(random)
Assay = EPM									
Holmes, 2003 Mice Female	11	16.26	14.21	13	5.16	5.830	1.02	[0.158; 1.88]	3.4%
Holmes, 2003 Mice Female	14	6.03	9.98	11	4.96	8.915	0.11	[–0.682; 0.90]	3.7%
Li, 2004 Mice Female	11	48.38	25.83	11	14.87	21.915	1.35	[0.403; 2.29]	3.1%
Carroll, 2007 Mice Female and Male	30	49.68	27.69	29	41.51	34.514	0.26	[–0.254; 0.77]	5.0%
Line, 2011 Mice Female and Male	9	10.82	6.62	7	2.94	5.601	1.20	[0.105; 2.30]	2.6%
Holmes, 2003 Mice Male	15	45.86	34.16	15	19.76	21.859	0.89	[0.131; 1.64]	3.9%
Holmes, 2003 Mice Male	11	12.30	7.61	10	1.40	2.833	1.79	[0.744; 2.83]	2.8%
Holmes, 2003 Mice Male	13	5.75	8.51	12	0.04	0.001	0.90	[0.068; 1.73]	3.6%
Kalueff, 2007 Mice Male	11	292.00	126.03	8	168.00	138.593	0.90	[–0.064; 1.87]	3.1%
Kalueff, 2007 Mice Male	11	48.67	21.01	8	28.00	23.099	0.90	[–0.064; 1.87]	3.1%
Lira, 2003 Mice Male	20	6.79	5.92	17	7.67	7.999	–0.12	[–0.771; 0.52]	4.4%
Schipper, 2011 Rats Female	5	38.45	10.52	5	18.58	5.521	2.14	[0.424; 3.85]	1.4%
Olivier, 2008 Rats Male	12	10.14	8.25	12	5.56	5.498	0.63	[–0.192; 1.46]	3.6%
Random effects model	173			158			0.78	[0.450; 1.10]	43.7%
Heterogeneity: I^2=45.3%, Tau^2=0.1572, p=0.0384									
Assay = LD									
Holmes, 2003 Mice Female	11	23.01	13.93	13	7.57	7.769	1.35	[0.450; 2.26]	3.3%
Holmes, 2003 Mice Female	14	5.33	6.51	11	6.46	11.361	–0.12	[–0.913; 0.67]	3.7%
Carroll, 2007 Mice Female and Male	30	47.98	14.17	29	32.93	20.900	0.83	[0.301; 1.37]	4.9%
Holmes, 2003 Mice Male	15	29.28	23.68	15	18.70	12.297	0.55	[–0.185; 1.28]	4.0%
Holmes, 2003 Mice Male	11	19.06	7.51	10	4.59	4.106	2.26	[1.122; 3.41]	2.5%
Holmes, 2003 Mice Male	13	3.76	7.47	12	1.05	2.967	0.45	[–0.343; 1.25]	3.7%
Random effects model	94			90			0.83	[0.171; 1.49]	22.1%
Heterogeneity: I^2=64.4%, Tau^2=0.5054, p=0.0154									
Assay = OF									
Kalueff, 2007 Mice Female	8	42.92	22.95	7	6.82	13.067	1.78	[0.531; 3.04]	2.2%
Carroll, 2007 Mice Female and Male	30	20.11	13.52	29	12.82	13.296	0.54	[0.016; 1.06]	5.0%
Zhao, 2006 Mice Female and Male	12	36.69	25.05	12	18.96	12.526	0.86	[0.021; 1.71]	3.5%
Zhao, 2006 Mice Female and Male	12	34.14	22.92	12	16.93	9.471	0.95	[0.096; 1.80]	3.5%
Holmes, 2003 Mice Male	14	39.63	11.88	14	17.17	15.401	1.59	[0.721; 2.45]	3.4%
Kalueff, 2007 Mice Male	11	64.00	19.90	8	37.00	22.627	1.22	[0.215; 2.23]	2.9%
Kalueff, 2007 Mice Male	11	42.07	9.04	8	25.16	11.333	1.61	[0.533; 2.68]	2.7%
Moya, 2011 Mice Male	10	55.97	18.96	10	22.70	10.410	2.08	[0.952; 3.22]	2.5%
Pang, 2011 Mice Male	25	54.68	31.75	28	48.68	28.003	0.20	[–0.343; 0.74]	4.9%
Olivier, 2008 Rats Male	12	29.72	15.89	12	15.61	16.191	0.85	[0.008; 1.69]	3.5%
Random effects model	145			140			1.01	[0.658; 1.36]	34.2%
Heterogeneity: I^2=52.3%, Tau^2=0.1309, p=0.0263									
Random effects model	**412**			**388**			**0.88**	**[0.648; 1.10]**	**100%**
Heterogeneity: I^2=50.3%, Tau^2=0.2011, p=0.0012									

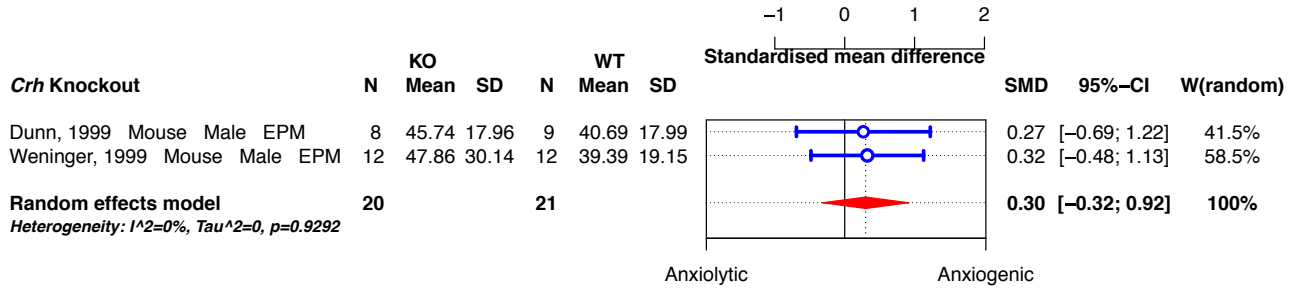
B



Htt Overexpression	OE N	OE Mean	OE SD	WT N	WT Mean	WT SD	SMD	95%–CI	W(random)
Jennings, 2006 Mouse Male EPM	8	15.52	14.63	8	30.69	12.31	–1.06	[–2.13; 0.005]	25.4%
Jennings, 2006 Mouse Male EPM	8	1.59	2.74	8	28.84	21.70	–1.67	[–2.85; –0.484]	22.7%
Line, 2011 Mouse Male and Female EPM	9	18.34	14.29	7	39.16	15.63	–1.32	[–2.44; –0.205]	24.2%
Jennings, 2006 Mouse Male OF	8	38.69	29.27	8	36.34	21.95	0.09	[–0.89; 1.067]	27.7%
Random effects model	**33**			**31**			**–0.94**	**[–1.69; –0.202]**	**100%**
Heterogeneity: I^2=51.1%, Tau^2=0.2678, p=0.1053									

Figure 5. Meta-analyses of serotonin transporter interventions on rodent anxiety-related behaviors. Meta-analysis of effect sizes of serotonin-targeted interventions is shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N), and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD).
Effects of: A. Serotonin transporter gene (*Htt*) knockout models B. *Htt* overexpression models.

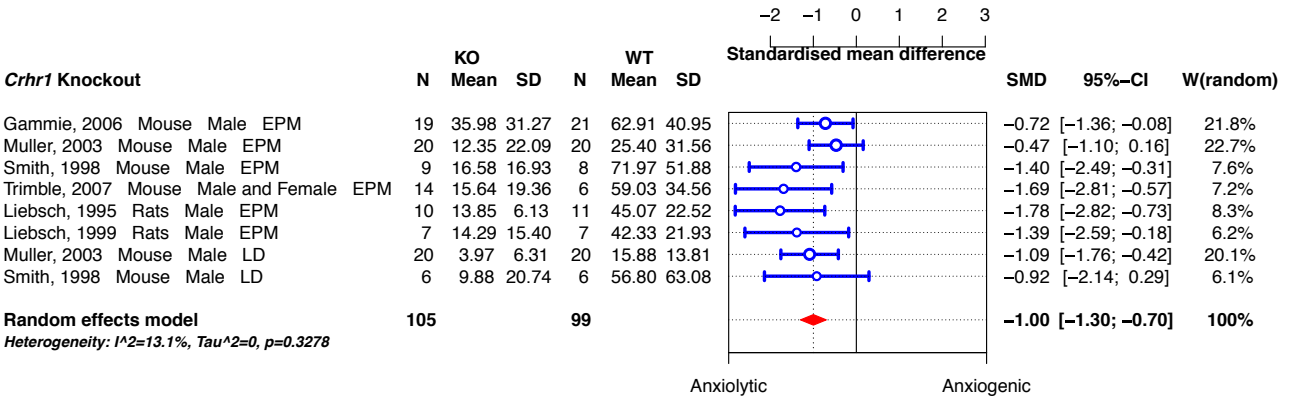
A



Crh Knockout	KO N	KO Mean	KO SD	WT N	WT Mean	WT SD	SMD	95%–CI	W(random)
Dunn, 1999 Mouse Male EPM	8	45.74	17.96	9	40.69	17.99	0.27	[–0.69; 1.22]	41.5%
Weninger, 1999 Mouse Male EPM	12	47.86	30.14	12	39.39	19.15	0.32	[–0.48; 1.13]	58.5%
Random effects model	**20**			**21**			**0.30**	**[–0.32; 0.92]**	**100%**

Heterogeneity: I^2=0%, Tau^2=0, p=0.9292

B



Crhr1 Knockout	KO N	KO Mean	KO SD	WT N	WT Mean	WT SD	SMD	95%–CI	W(random)
Gammie, 2006 Mouse Male EPM	19	35.98	31.27	21	62.91	40.95	–0.72	[–1.36; –0.08]	21.8%
Muller, 2003 Mouse Male EPM	20	12.35	22.09	20	25.40	31.56	–0.47	[–1.10; 0.16]	22.7%
Smith, 1998 Mouse Male EPM	9	16.58	16.93	8	71.97	51.88	–1.40	[–2.49; –0.31]	7.6%
Trimble, 2007 Mouse Male and Female EPM	14	15.64	19.36	6	59.03	34.56	–1.69	[–2.81; –0.57]	7.2%
Liebsch, 1995 Rats Male EPM	10	13.85	6.13	11	45.07	22.52	–1.78	[–2.82; –0.73]	8.3%
Liebsch, 1999 Rats Male EPM	7	14.29	15.40	7	42.33	21.93	–1.39	[–2.59; –0.18]	6.2%
Muller, 2003 Mouse Male LD	20	3.97	6.31	20	15.88	13.81	–1.09	[–1.76; –0.42]	20.1%
Smith, 1998 Mouse Male LD	6	9.88	20.74	6	56.80	63.08	–0.92	[–2.14; 0.29]	6.1%
Random effects model	**105**			**99**			**–1.00**	**[–1.30; –0.70]**	**100%**

Heterogeneity: I^2=13.1%, Tau^2=0, p=0.3278

Figure 6. Meta-analyses of the effects of stress signaling genes on anxiety-related behaviors. Meta-analysis of effect sizes of stress signaling genes, shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N), and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD). Effects of: A. *Crh* gene knockout. B. *Crhr1* gene knockout.

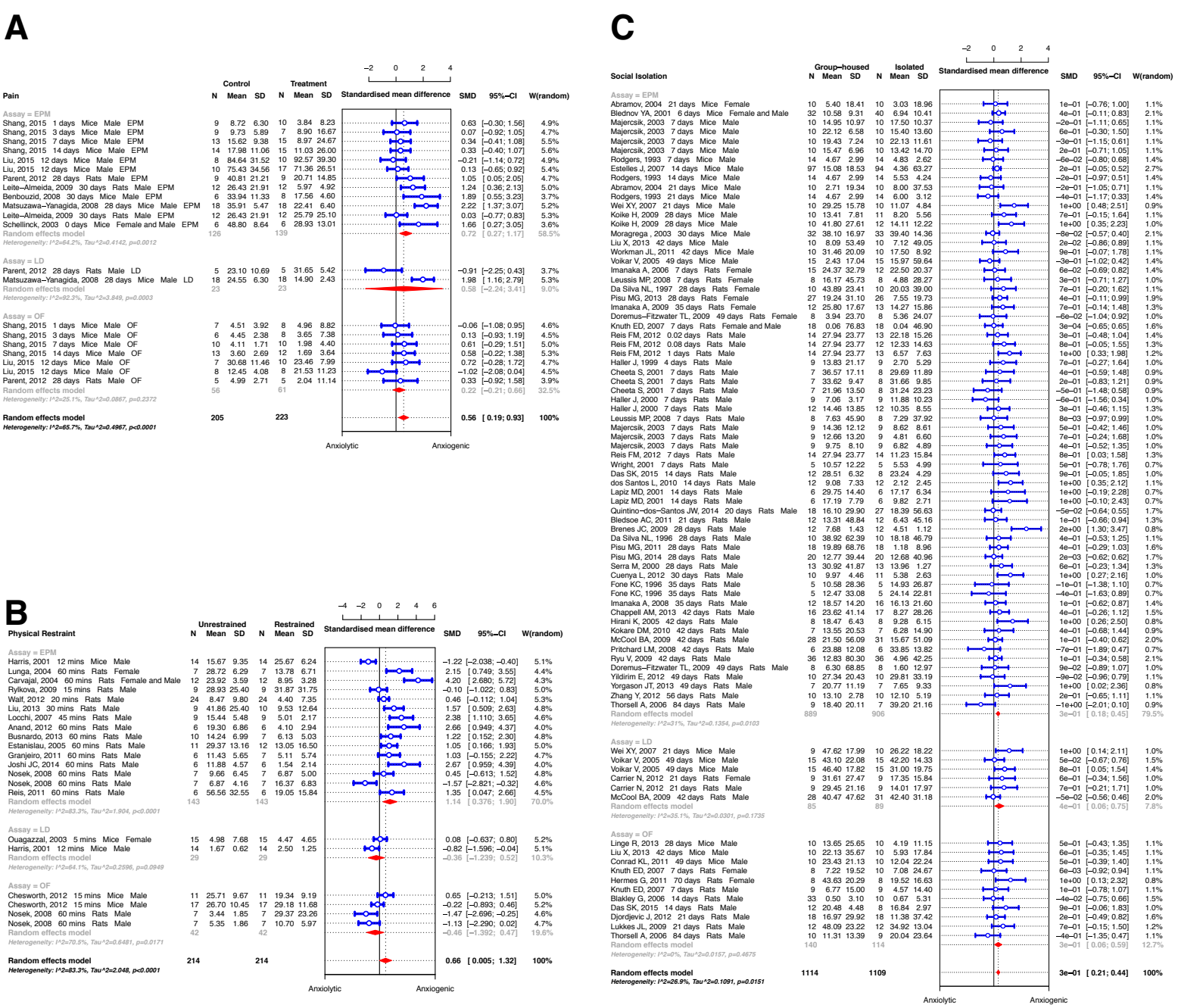


Figure 7. Meta-analyses of experiments on the stress-anxiety relationship in rodents.
Meta-analysis of effect sizes of stress-anxiety interventions is shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N), and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD).
Effects of: A. Acute pain. B. Physical restraint (immobilisation). C. Social isolation.

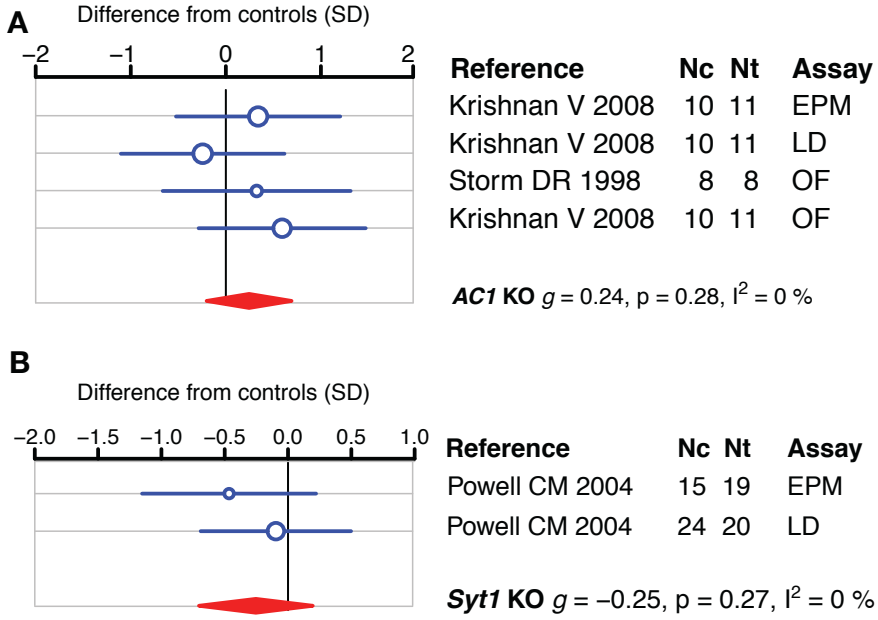


Figure 8: Interventions with no effect on anxiety-related behaviors. Meta-analysis of effect sizes of non-anxiety-related interventions, shown as a forest plot of standardized effect sizes (Hedges' *g*). Error bars indicate the 95% confidence intervals of *g*. The weighted average mean effect size of all studies is represented by the central vertices of a red diamond; the outer vertices indicate the 95% confidence intervals. Control and treatment samples sizes (N_C, N_T) and the assay types of the studies are given; elevated plus maze (EPM), open field (OF) and light-dark box (LD). Effects of: **A.** Adcy1 gene knockout models. **B.** Synaptotagmin gene (*Syt1*) mutation models.

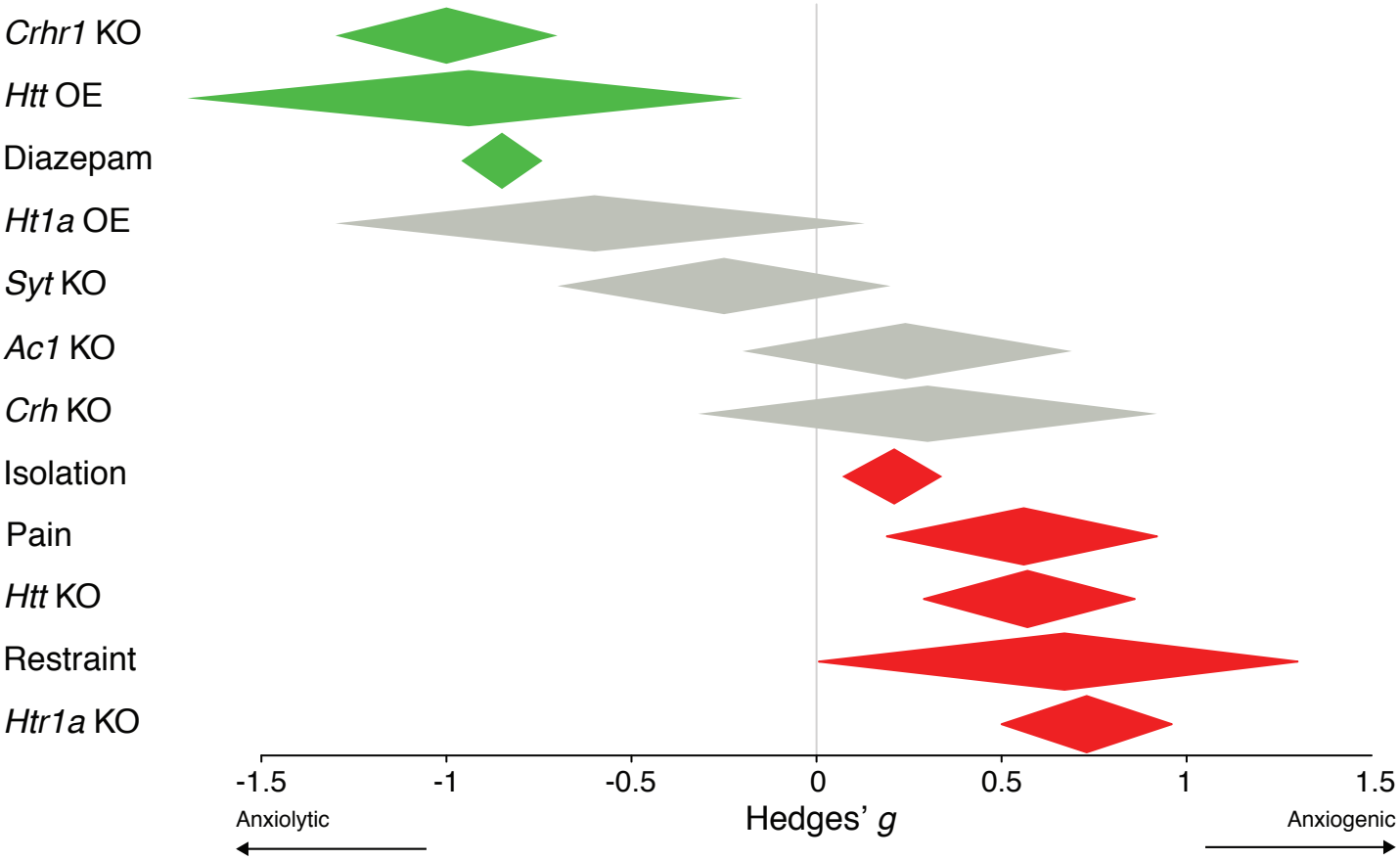


Figure 9. Summary effect sizes of all meta-analyses. The weighted mean effect sizes of all 12 interventions are shown here. Each mean effect size is represented by the central vertices of a diamond; the outer vertices indicate the 95% confidence intervals. The horizontal axis is Hedges' *g*, the standard deviation change relative to control animals. Color indicates direction (green = anxiolytic, red = anxiogenic) and statistical significance (grey = statistically non-significant). The diamonds for the diazepam, social isolation, and *Htt* KO meta-analyses represent the summary effect sizes after trim-and-fill bias correction.

Table 1. Summary of systematic reviews of anxiety-related interventions in mouse and rat. The PubMed query phrases used to identify articles that might contain data relevant to the interventions and assays of interest are detailed. Title, abstract and full-text searches were performed to identify articles meeting the selected criteria. Where there were fewer than ten articles meeting the selection criteria, all relevant data in all articles found were used for data extraction and meta-analysis. Where there were more articles, we took a random sample of ten papers and used only relevant data therein for meta-analysis.

Intervention	Query phrase used in PubMed for study selection	Articles identified by phrase	Articles meeting criteria	Articles in meta-analysis
Diazepam	((((diazepam OR valium)) AND anxiety) AND (open field OR exploratory)) AND (rodent OR rat OR rats OR mouse OR mice OR *Mus*)	540	172	172
***Ht1a* knockout**	(serotonin1A receptor OR 5-HT1A receptor AND knockout AND anxiety)	85	12	12
***Ht1a* over-expression**	(serotonin1A receptor) OR 5-HT1A receptor) AND (over-expression OR over-expression OR over-expressing) AND anxiety	13	3	3
***Htt* knockout**	(serotonin transporter knockout OR knockdown OR deletion OR antisense AND anxiety AND (elevated plus maze OR open field OR light-dark) AND (rats OR rat OR mice OR mouse OR *Mus*)	37	13	13
***Htt* over-expression**	(serotonin transporter AND anxiety AND (elevated plus maze OR open field OR light-dark) AND (increased OR over-expression OR overexpressing OR transgenic)) AND (rats OR rat OR mice OR mouse OR *Mus*)	65	2	2
***Crh* knockout**	(CRF OR CRH OR Corticotropin releasing factor AND knockout AND anxiety AND (elevated plus maze OR open field OR light-dark))) AND (rats OR rat OR mice OR mouse OR Mus)	62	2	2
***Crhr1* knockout**	(Corticotropin releasing factor receptor 1-deficient mice) OR CRH1 receptor antisense oligodeoxynucleotide OR Crhr1 null mutants OR Corticotropin-releasing hormone receptor antisense)	62	6	6
Pain	(Inflammatory pain AND anxiety OR neuropathic pain AND anxiety AND (elevated plus maze OR open field OR light-dark))) AND (rats OR rat OR mice OR mouse OR *Mus*)	49	7	7
Restraint	(acute restraint AND anxiety AND (elevated plus maze OR open field OR light-dark) AND (rats OR rat OR mice OR mouse OR *Mus*)	87	15	15
Isolation	(social Isolation OR single housing)) AND anxiety) AND (elevated plus maze OR plus-maze OR open field OR OFT OR light-dark)) AND (rats OR rat OR mice OR mouse OR *Mus*)	155	50	50
***Adcy1* knockout**	*Ad hoc* literature search	2	2	2
Synaptotagmin	*Ad hoc* literature search	1	1	1

Table 2. Summary of Meta-Analyses of Ten Anxiety-related Interventions and Two Non-anxiety-related Interventions in Rodents

Shown here are the summary effect sizes (Hedges' *g*) for the ten ARDEBs reviewed, alongside 2 non-ARDEB-related interventions (Ac1 KO and Syt KO) in rodents. I^2 — Heterogeneity of mixed-effects meta-analysis. KO — knockout, OE — Over-expression. Meta-analyses with more than 10 experiments were tested for publication bias with Egger's test. 95% confidence intervals (95% CI) are given in square brackers for Hedges' *g* (adjusted and unadjusted), as well as for I^2.

	No. of Experiments	No. of Studies	Hedges' *g* [95% CI]	p-value	I^2 [95% CI]	Egger's Test p-value	No. of Experiments Added After Trim-and-Fill	Adjusted Hedges' *g* [95% CI]	p-value Adjusted Hedges' *g*
Diazepam	386	172	-1.3 [-1.4; -1.2]	1.36e-144	70.4 [67.2; 73.3]	2.35e-56	102	-0.85 [-0.96; -0.74]	4.72e-56
Isolation	83	50	0.33 [0.21; 0.44]	3.37e-08	40.7 [3.5; 44.6]	0.0146	12	0.21 [0.069; 0.34]	0.00316
Htt KO	29	13	0.88 [0.65; 1.1]	5.18e-14	54.6 [23.7; 67.6]	6.72e-06	10	0.57 [0.29; 0.86]	9.71e-05
Restraint	21	16	0.67 [0.0062; 1.3]	0.0479	89.3 [75.8; 88.7]	0.0305	0	0.67 [0.0062; 1.3]	0.0479
Pain	21	7	0.56 [0.19; 0.92]	0.00283	68.1 [44.6; 78]	0.763	NA	NA	NA
Ht1a KO	20	11	0.73 [0.5; 0.96]	3.15e-10	46.6 [0; 58.2]	0.545	NA	NA	NA
Ht1a OE	8	3	-0.6 [-1.3; 0.13]	0.105	82.7 [61.8; 89.8]	NA	NA	NA	NA
Crhr1 KO	8	6	-1 [-1.3; -0.7]	6.64e-11	0 [0; 55.7]	NA	NA	NA	NA
Htt OE	4	2	-0.94 [-1.7; -0.2]	0.0127	46.8 [0; 83.8]	NA	NA	NA	NA
Ac1 KO	4	2	0.24 [-0.2; 0.69]	0.284	0 [0; 75.9]	NA	NA	NA	NA
Crh KO	2	2	0.3 [-0.32; 0.92]	0.34	0 [NA; NA]	NA	NA	NA	NA
Syt KO	2	1	-0.25 [-0.7; 0.2]	0.268	0 [NA; NA]	NA	NA	NA	NA