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

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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This meta-analysis excluded unpublished and non-English studies; publication bias and heterogeneity were identified in several meta-analyses.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] , $p = 3.5 \times 10^{-10}$) 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], $p = 6.64 \times 10^{-11}$; 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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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

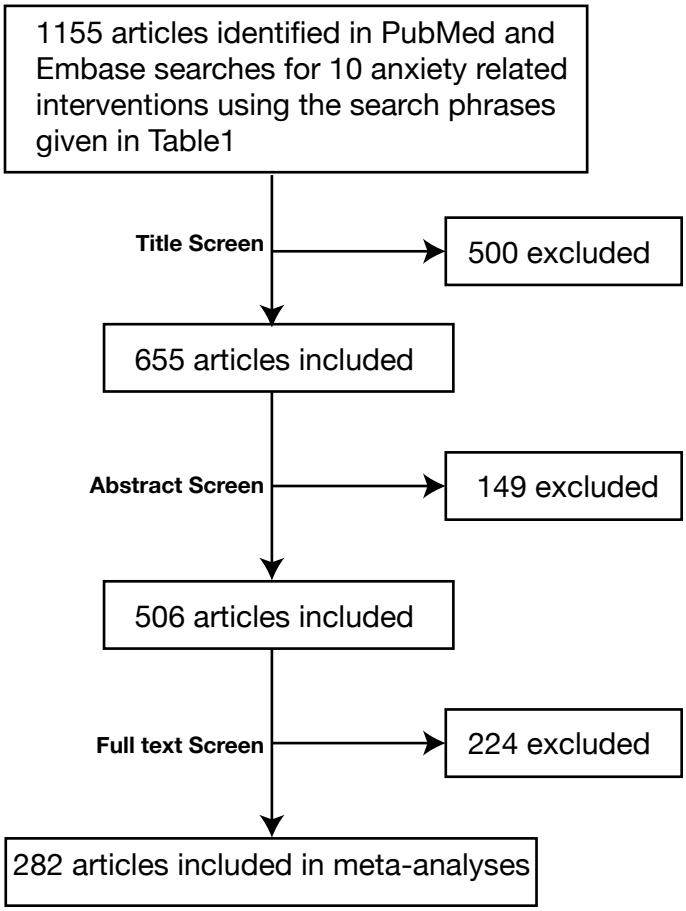


Figure 1. Flow chart of the systematic literature review of 10 anxiotropic interventions. The literature was reviewed in a four-stage process, starting with a PubMed search that yielded 1156 articles, followed by three screens of increasing detail, reviewing the article title, abstract, and full text 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.

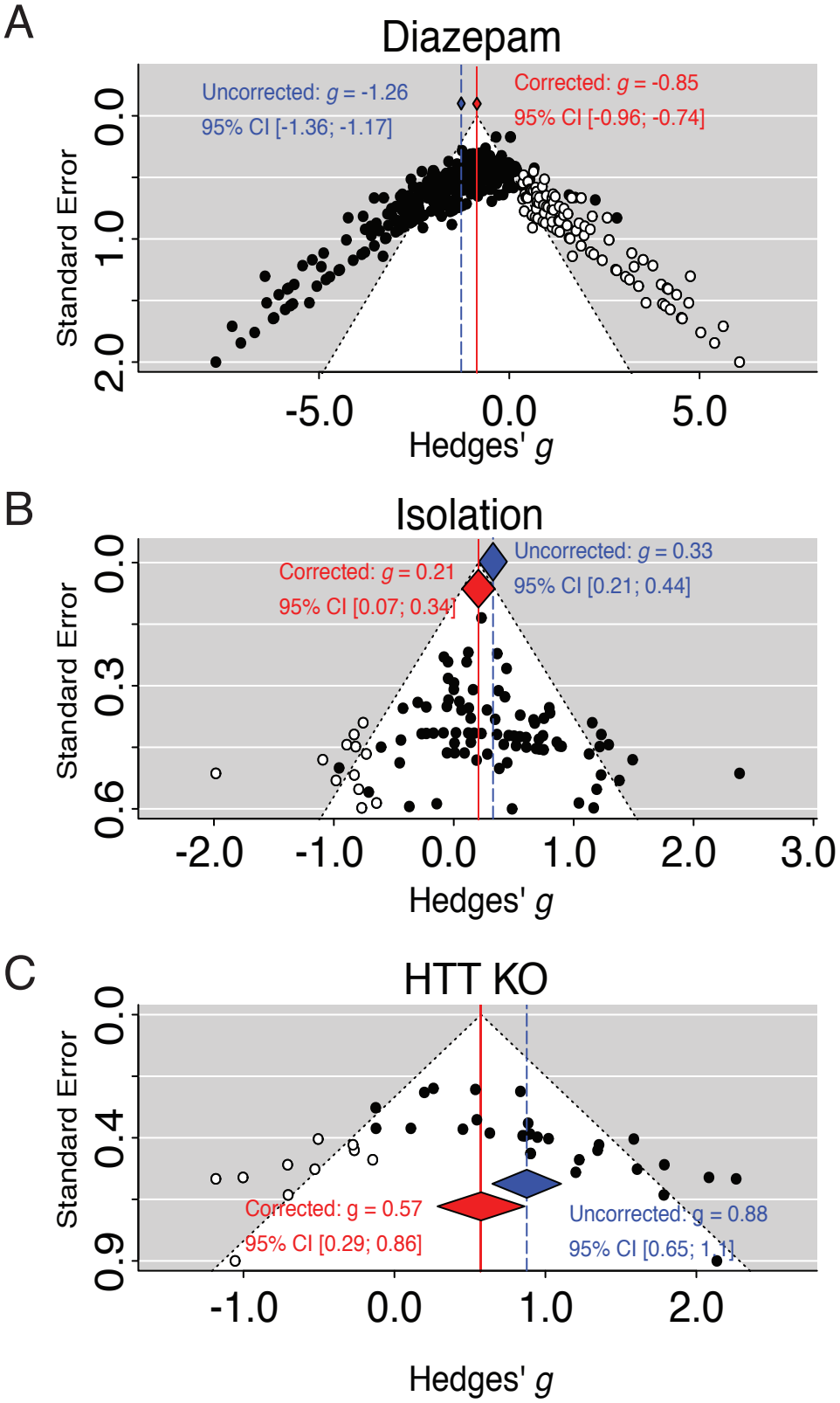


Figure 2. Funnel Plots for Three Meta-Analysis With Evidence of Publication Bias. Where at least ten experiments were available for meta-analysis, the effect sizes (Hedges' g) of the experiments are plotted against their respective standard errors. Points on each plot represent individual experiments. 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.

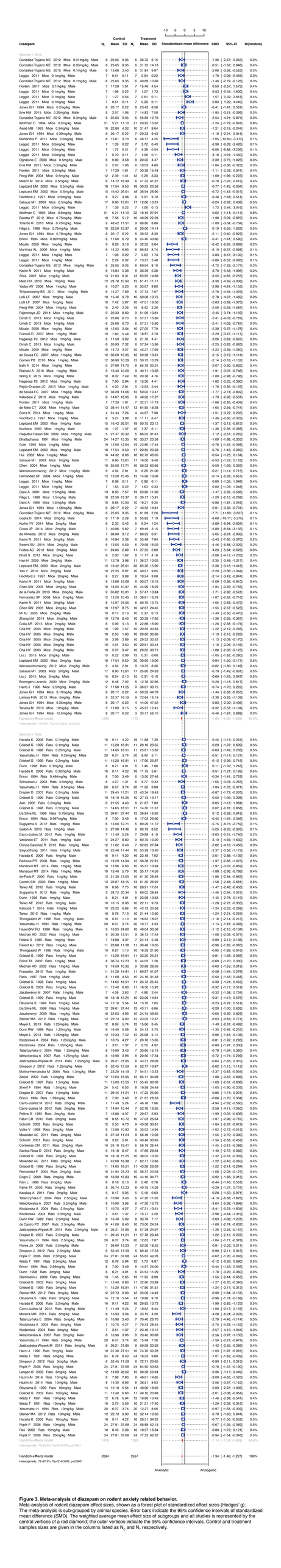
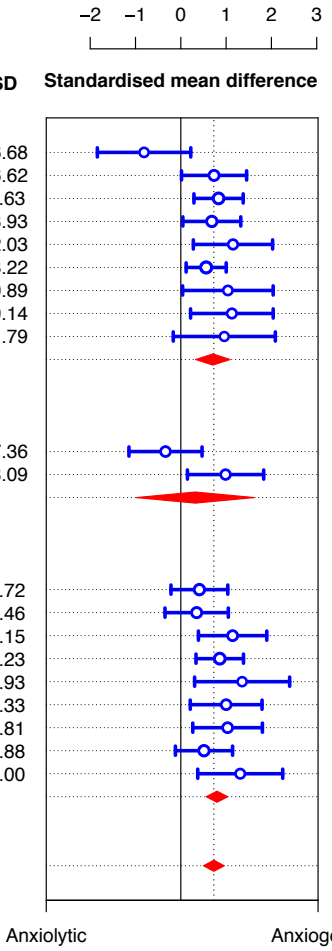


Figure 3. Meta-analysis of diazepam on rodent anxiety related behavior.
Meta-analysis of rodent diazepam effect sizes, shown as a forest plot of standardized effect sizes (Hedges' g). The meta-analysis is sub-grouped by animal species. Error bars indicate the 95% confidence intervals of standardized 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									

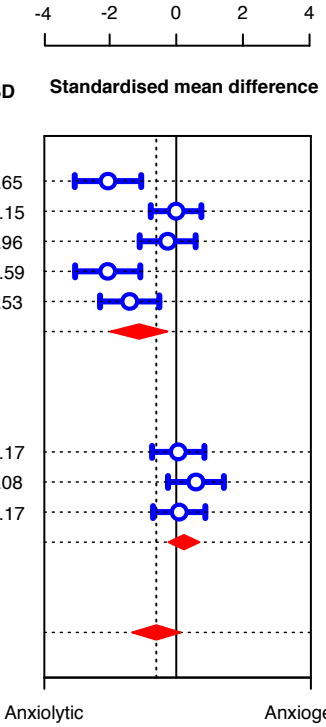
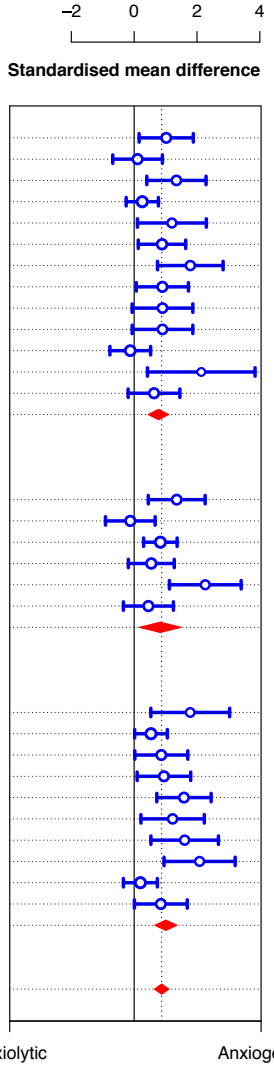


Figure 4. Meta-analyses of serotonin receptor interventions on rodent anxiety-related behaviors. Meta-analysis of effect sizes of serotonin-targeted interventions is shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted average 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									

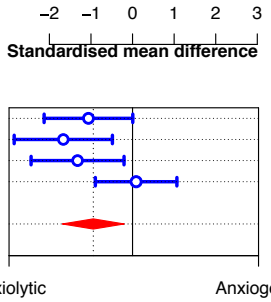
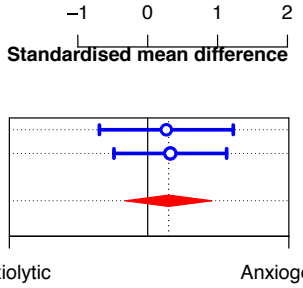


Figure 5. Meta-analyses of serotonin transporter interventions on rodent anxiety-related behaviors. Meta-analysis of effect sizes of serotonin-targeted interventions is shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted 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

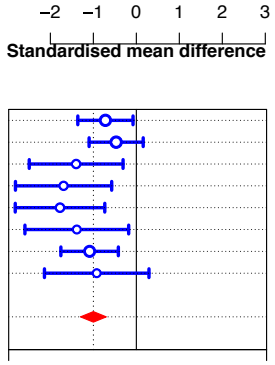


Figure 6. Meta-analyses of the effects of stress signaling genes on anxiety-related behaviors. Meta-analysis of effect sizes of stress signaling genes, shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect 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.

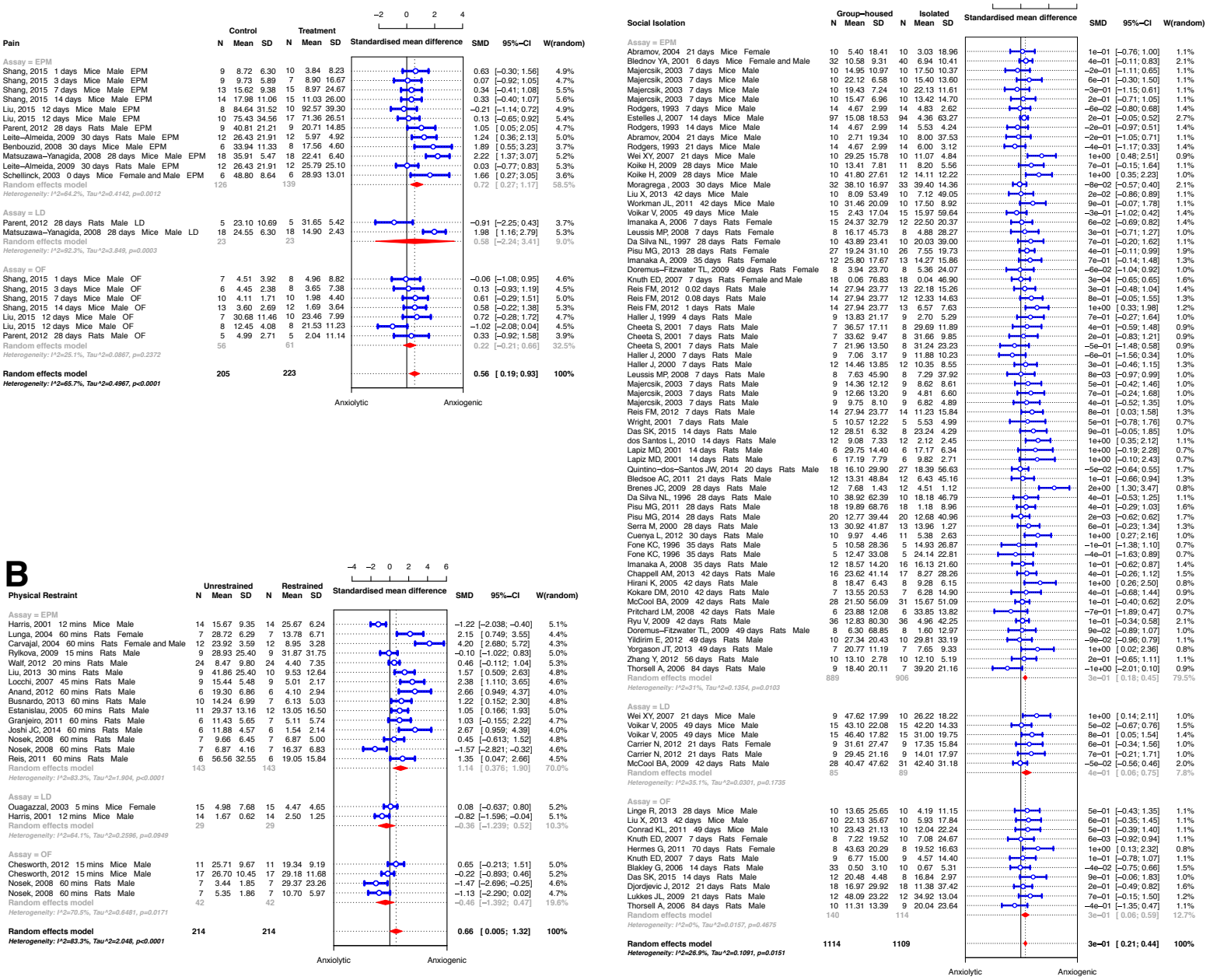


Figure 7. Meta-analyses of experiments on the stress-anxiety relationship in rodents.
Meta-analysis of effect sizes of stress-anxiety interventions is shown as a forest plot of standardized effect sizes (Hedges' g). Error bars indicate the 95% confidence intervals of g. The weighted average mean effect 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.

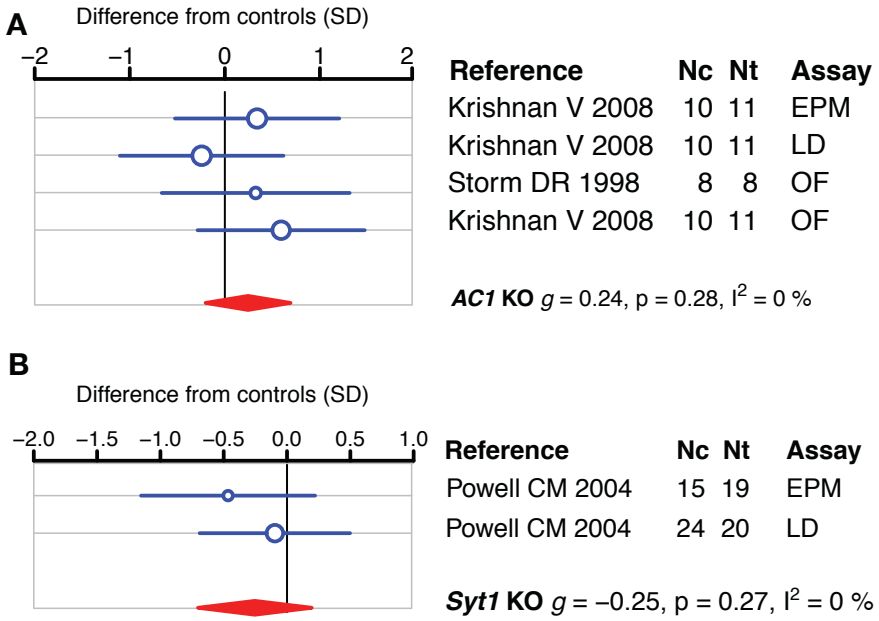


Figure 8: Interventions with no effect on anxiety-related behaviors. Meta-analysis of effect sizes of non-anxiety-related interventions, shown as a forest plot of standardized effect sizes (Hedges' *g*). Error bars indicate the 95% confidence intervals of *g*. The weighted average mean effect size of 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.

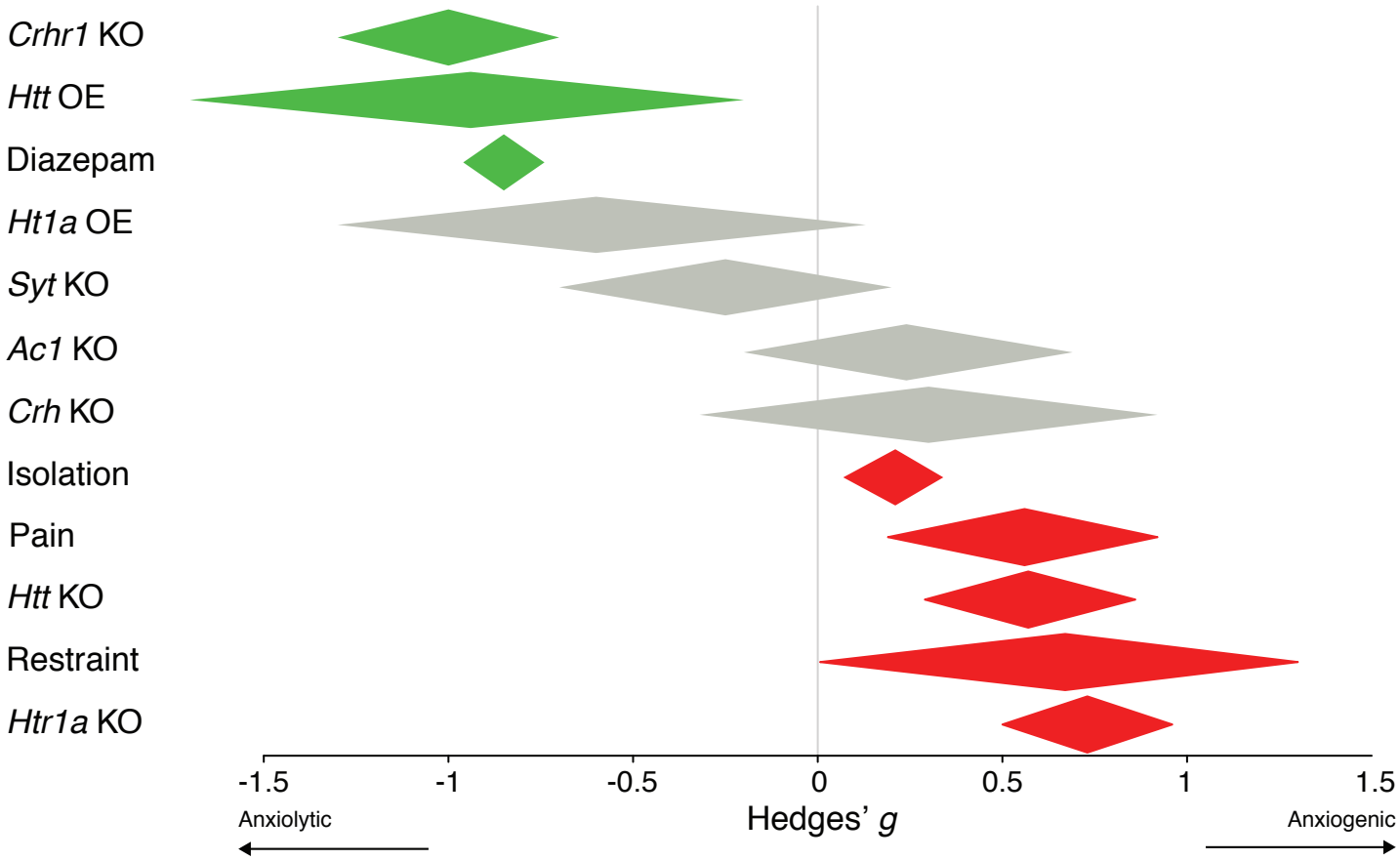


Figure 9. Summary effect sizes of all meta-analyses. The weighted mean effect sizes of all 12 interventions are shown here. Each mean effect size is represented by the central vertices of a diamond; the outer vertices indicate the 95% confidence intervals. The horizontal axis is Hedges' *g*, the standard 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