Reliability of the chronic mild stress model of depression: A user survey
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ABSTRACT
The chronic mild stress (CMS) model of depression is considered by many to be the animal model of depression that has the greatest validity and translational potential, but it has often been criticized for a perceived lack of reliability. The aims of this study were to establish the extent to which the procedure is reproducible, and to identify experimental variables relevant to its reliability. Because failures to replicate frequently remain unpublished, a survey methodology was used. A questionnaire was circulated to 170 labs identified from a PubMed search as having published a CMS study in the years 2010 or 2015 (with no selection in respect of the results reported). Responses were returned by 71 (42%) of the recipients, followed by further correspondence with some of them. Most of the respondents (n = 53; 75%) reported that the CMS procedure worked reliably in their hands. Of the others, 15 (21%) reported that the procedure was usually reliable, but not always (n = 9; 13%) or not for all measures (n = 6; 8%). Only three respondents (4%) reported being unable to reproduce the characteristic effects, two of whom may be using an insufficient duration of CMS exposure. A series of analyses compared the 75% of ‘reliable’ labs with the 25% of ‘less reliable’ labs on a range of experimenter, subject, stress and outcome variables. Few if any significant differences between these two samples were identified, possibly because of the small size and diversity of the ‘less reliable’ sample. Two other limitations of the study include the (unavoidable) omission of labs that may have worked with the model but not published their data, and the use of ad hoc measures to compare the severity of different stress regimes. The results are discussed in relation to relevant published observations. It is concluded that CMS is in fact a rather robust model, but the factors that result in a less effective implementation in a minority of laboratories remain to be firmly established.

1. Introduction
Chronic mild stress (CMS) is a well-validated and widely used animal model of depression, based on the loss of responsiveness to rewards by animals subjected to a varying schedule of minor stressors. The CMS model was developed in the late 1980s, on the basis of an earlier observation that rats subjected to a variety of relatively severe stressors failed to increase their fluid intake when sucrose or saccharin was added to their drinking water (Katz, 1982). The aims of the early CMS work were: to engender similar effects using a much more mild and ecologically valid stress regime; to explore the concept of stress-induced anhedonia by investigating the effects of CMS on a variety of reward-related behavioural endpoints; and to confirm the utility of the model as a test-bed in which to investigate the mechanisms of action of antidepressant drugs (Willner et al., 1987, 1992). The CMS procedure was implemented by exposing rats (or later, mice: Monleon et al., 1994) to a relatively continuous variety of mild stressors, such as periods of food and water deprivation, changes of cage mates, and other similarly innocuous manipulations. Over a period of weeks of chronic exposure the animals gradually reduced their consumption of, and preference for, a preferred dilute sucrose solution, and this deficit could be reversed by chronic, but not acute, treatment with antidepressant drugs. The development and validation of the CMS model are described in more detail in earlier reviews, and in the accompanying paper (Willner, 1997a, 2005, 2016).

As the CMS model was taken up by other labs in the early 1990s,
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1. Introduction

1.1. Background

Chronic mild stress (CMS) is a well-established animal model of depression, which has been used extensively in research to investigate the effects of stress on various biological and behavioral outcomes. This model involves repeated exposure to mild stressors, such as maternal separation, restraint, or noise, over a prolonged period. The rationale behind using CMS is to mimic the chronic stressors experienced in daily life, which are thought to contribute to the development and maintenance of depression.

Prior to the use of CMS, the model was first described by Porsolt et al. (1978), who observed that rats exposed to chronic stress showed decreased sucrose intake and increased immobility in the forced swim test (FST) compared to control animals. Since then, CMS has been widely used in research, and numerous studies have reported various behavioral and physiological changes in response to chronic stress exposure.

Despite its widespread use, CMS has faced criticism regarding its reliability and reproducibility. Several studies have reported variability in the outcomes of CMS experiments, leading to calls for more rigorous evaluation of the model’s reliability. This has prompted the current study, which aimed to assess the reliability of CMS across different laboratories and to identify factors that may influence its performance.

2. Methods

2.1. Survey methodology

An initial PubMed search using the search terms “chronic (mild or varied or unpredictable) stress” returned over 3000 hits. In order to narrow this literature down, the search was repeated for single years at 5-year intervals from 1990 to 2015 (with the final search on December 31, 2015), and the outputs were searched by hand to identify papers involving varied stress regimes in animals. Studies in people and animal studies involving repeated presentation of a single stressor were excluded. This search indicated an exponential increase in publications, rising above 100 in 2010. The years 2010 and 2015 were chosen for further investigation, on the basis that authors publishing in 2015 had recent experience with the CMS methodology, while those publishing in 2010 might have encountered difficulties that had caused them to cease working with the model, but should still have a good memory of their experiences. Papers from 2010 and 2015 were ordered by country and region, in order to identify independent laboratories, and email addresses were collected where easily available from PubMed abstracts or open access publications, supplemented in a few cases by addresses already known to the author.

Each of the labs for which an email address was identified was sent a survey, created using Google Forms, and asked to return it via a web link. A total of three further requests were made to non-responders. Following receipt of an email explaining that Google was not readily available in China, the second and third requests to Chinese recipients invited them to return the survey via email; this offer was also extended to other respondents at the third request. The survey covered the basics of the methodology used, followed by sections probing within-experiment reliability and between-experiment reliability. The survey is not presented in detail because many of the questions returned indeterminate answers, such as a high proportion of missing or ambiguous responses. Details of the questions for which responses could usefully be analyzed are presented in the Results section.

Subsequently, follow-up questionnaires were emailed (i) to respondents who indicated that in their lab the procedure was “usually reliable but not always”, to probe the nature of unreliable performance and potential differences between more and less successful experiments, and (ii) to respondents who indicated that they did not use a sucrose intake or preference test. Again, details of the questions asked are presented in the Results section.

2.2. Estimation of CMS intensity

In order to compare the severity of different stress regimes, a two-stage Delphi procedure was used to obtain ratings from five experts with extensive use of the CMS procedure. A list of 26 micro-stressors was compiled from responses to the survey, each of which was rated independently by the five raters, using a 5-point scale of severity. The ratings were then shared, anonymously, with the other raters, together with a few comments made on the first round. The ratings were then repeated, this time with separate ratings for rats and mice. Kendall’s coefficient of concordance was used to assess the degree of agreement between the five raters. Concordance was relatively low on the first round (W = 0.45, p < 0.001), and increased somewhat on the second round but remained below the minimum acceptable level of 0.6 (rats: W = 0.53; mice: W = 0.59). Considering that the raters included two rat experts and two mouse experts, plus the author, the concordance was calculated for three raters for each species (the two relevant experts plus the author). Both analyses achieved concordances of W = 0.75 (p < 0.001). The median of these three
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