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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 Because failures to replicate frequently remain unpublished, a survey methodology was used.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.

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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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concerns began to emerge about the reproducibility of the effects reported. Inter alia, this concern was highlighted by the fact that the procedure became less reliable in the hands of the original research group following a move to a different university. These issues, and others, were debated in detail in a Special Issue of the journal Psychopharmacology, which included a candid account of the first decade of CMS research (Willner, 1997a) and sixteen peer commentaries. The response to the peer commentaries summarized the position regarding the reliability of the CMS model as follows: "some laboratories, including, currently, our own, have experienced difficulty in (re)establishing the CMS procedure, but there are many other laboratories in which the procedure operates reliably" (Willner, 1997b). A later review summarized data from over a hundred labs reporting depressive-like (and antidepressant-reversible) effects of CMS across a wide range of depression-relevant end-points, including sucrose or saccharine intake or preference, sweet food intake, approach to sweet food, place conditioning using a variety of drug and natural reinforcers, brain stimulation reward, immobility in the forced swim test, learned helplessness, male aggression and sexual behaviour, grooming, and REM sleep latency (Willner, 2005). However, that review also identified a handful of studies, including several published only as meeting abstracts, reported 'anomalous' effects of CMS, such as increased sucrose intake or brain stimulation reward (Willner, 2005).

Partly as a result of the uncertainty described in the 1997 and 2005 review papers, there has been a frequently expressed assumption that the CMS procedure is unreliable or difficult to replicate, and reviews of animal models of depression typically include a statement to this effect. However, this conclusion does not sit comfortably alongside the burgeoning CMS literature, which, as described in the accompanying paper, now amounts to in excess of 1300 publications, that in the year 2015 alone include 230 papers from 180 labs in 30 countries (Willner, 2016). These statistics, and the exponentially increasing uptake of the CMS model (Willner, 2016), suggest that the model may be more reliable than is typically assumed. The aims of the present study were to attempt to quantify the extent to which the CMS model is reliable and to understand some of the relevant factors. The main focus was on the reliability with which CMS elicits the most widely used outcome, a decrease in sucrose intake or preference.

Investigating the reliability of an experimental procedure presents particular problems because of the possibility that the published literature represents the tip of an iceberg, with failures to replicate and other evidence of unreliability lying below the surface, unpublished. In order to take account of this issue, the present study adopted a survey methodology in preference to a systematic literature review, on the assumption that asking users about their experience of working with the CMS procedure would be more likely to yield insights into the problems they might have encountered. Another methodological issue that needed to be addressed at the outset is that different labs refer in different ways to procedures that may be similar or may diverge: alongside CMS, other labels include chronic unpredictable stress (CUS) and unpredictable chronic stress (UCS), chronic unpredictable mild stress (CUMS) and unpredictable chronic mild stress (UCMS), and chronic varied or variate stress (CVS). It was decided to take an inclusive approach to the survey, and this decision was vindicated by the outcome: an analysis presented in the accompanying paper (Willner, 2016), shows that empirically – and perhaps surprisingly – these different labels carry no information about the severity of the stress protocol and almost no information about the predictability of stress. In this paper, therefore, CMS is used as a generic term covering all of these procedures.

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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