Rodent Big Brother: A Home Cage Automated Behavioural Monitoring System for Safety Pharmacology and Toxicology Studies

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Introduction

In 2011 AstraZeneca set a challenge under the NC3Rs inaugural CRACK IT scheme, calling for novel technology to record locomotor activity, behaviour and temperature of individual rats continuously for up to 30 days for toxicology studies. The main objective was to develop a method to assess rats non-invasively, when group-housed in standard individually ventilated cages (IVC).

Objective

The measurement of locomotor activity has been available for several decades, but requires rats to be singly-housed in bespoke arenas for brief recording periods. Behavioural analysis generally requires manual observation by experienced observers, usually limited to ‘snapshots’ during the light phase when rats are less active (e.g. FOB, Irwin test). Body temperature can be measured manually at intervals, or continuously using surgically implanted telemetry transducers. The conventional approaches are not always compatible with 24 h continuous monitoring or with being performed concurrently in a repeat-dose study. The Rodent Big Brother system was developed to provide ubiquitous technology that can be incorporated into standard IVC racks rather than as a bench top system.

Methods

- Male Han Wistar rats (250-270 g) were each implanted with a radiofrequency identification (RFID) microchip subcutaneously in the flank region and housed in groups of 3 per cage.
- The system generates positional information and temperature via the RFID microchip, detected by a baseplate reader under the cage.
- Using Q statistic, a χ² periodogram can quantify how regular a circadian frequency is.
- Behaviours were captured via high-resolution camera using infrared lighting situated above each cage.
- The behaviour of singly-housed rats was annotated manually to train software to ultimately enable automatic recognition of common behaviours.

Figure 1. Schematic diagram of the enclosure

Results

- The system generates positional information and temperature via the RFID microchip, detected by a baseplate reader under the cage.
- Using Q statistic, a χ² periodogram can quantify how regular a circadian frequency is.
- Behaviours were captured via high-resolution camera using infrared lighting situated above each cage.
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Table 1. The 5 most common behaviours in a single-housed rat over a 1 h period during the light and dark phases. Annotation of 1 h of video takes ~2 h per rat.

<table>
<thead>
<tr>
<th>Behaviour</th>
<th>Night</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raoring</td>
<td>70</td>
<td>7</td>
</tr>
<tr>
<td>Drinking</td>
<td>26</td>
<td>3</td>
</tr>
<tr>
<td>Grooming: licking/chewing fur</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Gnawing chew stick</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Grooming: face washing</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 2. The high quality infrared side-on video enables capture and identification of animal behaviours 24/7.

Figure 3. Group mean temperature from 6 rats with 3 per cage. Data collected from the individual RFID microchips by the baseplate reader.

Figure 4. Subcutaneous temperature of rats when single-housed vs. group-housed during the dark phase. Group mean (±SEM) data plotted. Rats were single-housed at 16:00 and re-grouped at 08:00 the following day. There was a significant reduction in subcutaneous temperature from 1 h after separation from cage mates and throughout the 16 h separation period (\( P < 0.05 \), \( P < 0.01 \); paired t-test). The change in temperature illustrates the significance of group-housing for the welfare of animals.

Figure 5. A χ² periodogram of baseline activity data. The “robustness” of a rhythm is described as how regular a circadian rhythm is. The Q statistic is used as a numerical index of robustness. The high-frequency noise is filtered out and the value of the Q statistic determined reflects the extent of stationarity of the time series. The robustness of a circadian rhythm is an index of its stationarity. The peak is at 24h, indicating circadian frequency.

Figure 6. The webcam video captures the bird’s eye view of the cage and enables identification of animal’s location (used for baseplate validation only).

Figure 7. Subcutaneous empty pocket displays site of former localisation of RFID microchip. No or slight cellular reaction (focal chronic reactive granulation tissue) was observed histologically after H&E staining of skin collected from the flanks of all rats.

Conclusions

- We have developed new technology that is able to record locomotor activity, behaviour and subcutaneous temperature of individual rats simultaneously when group-housed in their standard home cage.
- Automated behaviour recognition software will enable adverse behavioural changes to be detected continuously, which is especially useful during the night.

Ongoing work to improve on the prototype

- Optimise subcutaneous RFID microchip location and orientation for maximal readout from baseplate and to optimise accuracy during low activity levels
- Validate software for automated behavioural analysis (seizure behaviour currently being recorded at Aston University, UK)
- Pharmacological validation

Once this is completed, 3Rs benefits will include being able to greatly increase the information content of existing study types to assess effects of compounds on activity, behaviour and temperature, without requiring surgery, and the potential to reduce the number of animals needed overall.

References


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