Continuous monitoring of individual rats when group-housed in the home cage to assess drug-induced changes in activity and temperature

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Control number: 668

Introduction

Conventional approaches for measuring the activity of rats necessitate single housing, which affects their behaviour and welfare. A subcutaneous radiofrequency identification (RFID) transponder was used to measure ambulatory activity and temperature of individual rats when group-housed in conventional, rack-mounted home cages (Fig. 1). The transponder location and temperature is detected by a matrix of 12 antennae in a baseplate under each cage per enclosure (Fig. 1). A high definition (HD) camera acquires side-view video of the cage to capture each animals' behaviours (Fig. 1). Baseplate-derived ambulatory activity correlates well with manual tracking and with side-view video pixel movement[1]. We have demonstrated the system can detect the sedative and hypothermic effects of chlorpromazine[1]. The objective of the current study was to evaluate whether the system can detect the stimulant and hyperthermic effects of (+)-amphetamine.

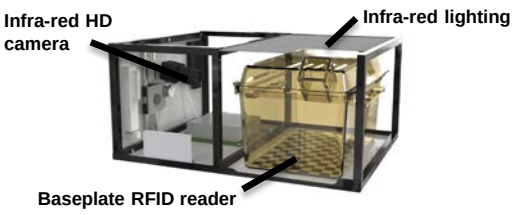


Figure 1: A schematic diagram of an enclosure set up in a conventional cage rack.

Methods

- Male Han Wistar rats (200-275g) were implanted with RFID transponders (Biothermo13, Biomark) subcutaneously in the ventral midline region (Fig. 2) and housed in groups of 3/cage with a 12h:12h light cycle (lights on at 07:00h)

Figure 2. Location of ventral midline RFID transponder in a Han Wistar rat

- (+)-Amphetamine (10 mg/kg oral) or its vehicle (sterile water; 10 mL/kg oral) on separate experimental conditions during the light and dark phases with 24h continuous monitoring using ActualHCA™ (Actual Analytics, UK).
  - **'Light phase'**; dosed at 09:00h
  - **'Cage change'**; dosed at 09:00h, cage change at T_{max} (2h post-dose)
  - **'Dark phase'**; dosed at 20:00h
- Cages were assigned to treatment groups based on the baseline activity data (number of transitions) collected 2 days before dosing.
- Activity data were derived from baseplate readings after filtering to remove any noise artefacts.
- Activity data (number of transitions between adjacent antenna) was correlated with motion detection acquired by the side-view camera to verify real activity (Fig. 6). Motion detection was captured by pixel movement from each frame of the video footage (frame rate set as 25 frames per second).
- Post-hoc manual home cage observation from the video footage of the 'light phase' session was carried out. Time-points were chosen based on the activity data.

Results

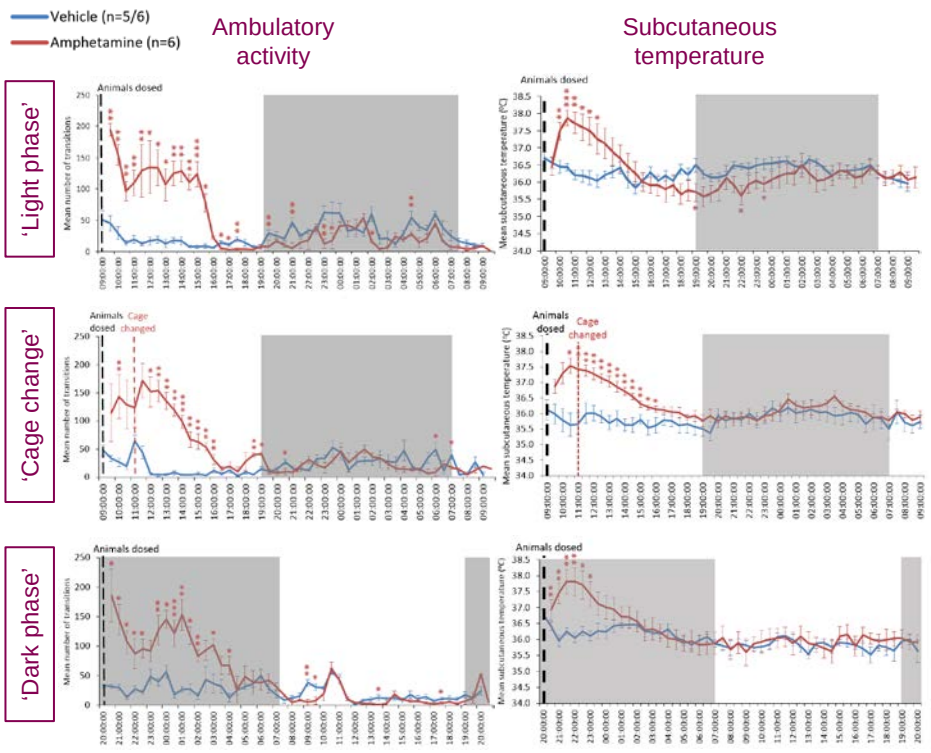


Figure 3. Mean (±SEM) ambulatory activity and temperature from the RFID transponder in (+)-amphetamine and vehicle treated animals for all 3 separate experimental conditions (n=5/6 per group). Grey shadings represents the dark phase (19:00h to 07:00h). Dotted black lines indicate when the animals were dosed and dotted red lines indicate where cage changed had occurred. Activity and temperature measurements were compared statistically with the vehicle group using t-test *(* P<0.05; ** P<0.01; *** P<0.001).*

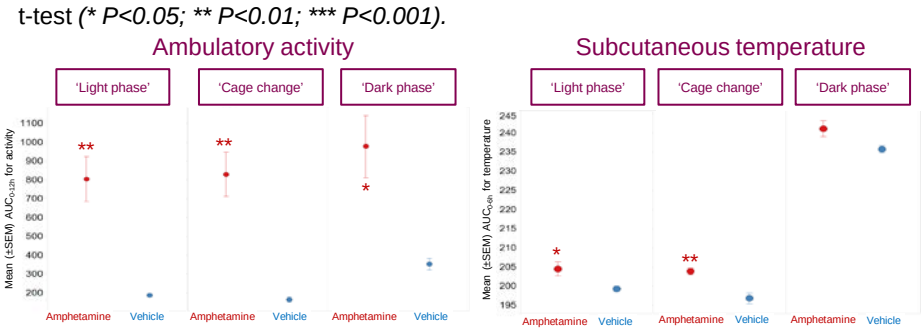


Figure 4. Mean (±SEM) $AUC_{0\text{-}12h}$ for ambulatory activity and $AUC_{0\text{-}6h}$ for temperature from the RFID transponder in (+)-amphetamine and vehicle treated animals for all 3 separate experimental conditions (n=5/6 per group). The $AUC_{0\text{-}12h}$ were compared statistically with the vehicle group using non-parametric Wilcoxon test *(* P<0.05; ** P<0.01).*

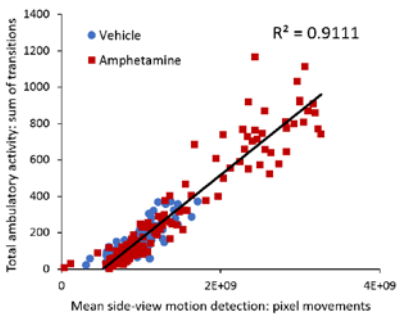
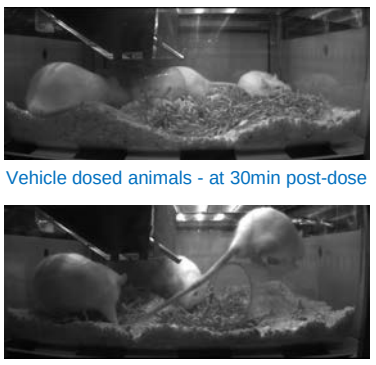


Figure 5. Motion detection from the side-view HD camera against baseplate-derived activity for both vehicle and amphetamine dosed animals in all 3 experimental conditions. The plot contains a total of 294 data points.

Time observed (post-dose)	Spontaneous activity increased	Spontaneous activity decreased	Sniffing increased	Rearing increased	Piloerection
15 min	**6/6**	0/6	**6/6**	**6/6**	0/6
30 min	**6/6**	0/6	**6/6**	**6/6**	**3/6**
60 min	**6/6**	0/6	**6/6**	**4/6**	1/6
120 min	**6/6**	0/6	**5/6**	**3/6**	0/6
240 min	**6/6**	0/6	**5/6**	2/6	0/6
480 min	0/6	2/6	0/6	0/6	0/6
720 min	0/6	**3/6**	0/6	0/6	0/6
840 min	0/6	**3/6**	0/6	0/6	0/6
1440 min	0/6	0/6	0/6	0/6	0/6

Table 1. Post-hoc manual home cage observation from video footage of animals from the 'light phase'. Animals dosed with amphetamine were compared with vehicle-dosed animals. Frequencies of amphetamine-dosed animals exhibiting the observation was recorded. Effects were considered significant if half or more of the animals in a given dose group exhibited the symptom. Significant effects are shown in **bold**.



Vehicle dosed animals - at 30min post-dose

Amphetamine dosed animals - at 30min post-dose

Figure 6. Side-view HD infra-red camera view of the video footage.

Conclusions

- The baseplate detected significantly increased ambulatory activity ($AUC_{0\text{-}12h}$ $P<0.05$) in all conditions, and subcutaneous temperature ($AUC_{0\text{-}6h}$ $P<0.05$) when dosed in the 'light phase' with or without 'cage change', in amphetamine-dosed animals (10 mg/kg, oral) compared to the vehicle-dosed animals.
- Motion detection data correlated well with the baseplate-derived activity data ($R^2 = 0.91$), verifying the activity measured by the baseplate.
- The HD video captured from the enclosures allows a trained observer to collect home cage observations of individual rats at any time of day or night.
- Increased spontaneous activity, rearing and sniffing observed is consistent with published literature[2].
- Decreased spontaneous activity was detected by the baseplate compared to the vehicle dosed animals in the 'light phase' from 7 hours post-dose and verified by the video observation.
- A compensatory decrease in spontaneous activity has not been reported in the literature as an amphetamine effect in rats.
- Continuous monitoring of rats can investigate the full behavioural profile of a drug.
- Capability to monitor individual rats when group-housed in home cage has a positive welfare impact.

References

1. Tse et al., (2016) Safety Pharmacology Society 16th Annual Meeting, Vancouver BC, Canada (Proceedings)
2. Eichler et al., (1980) Psychopharmacology 68, 297-290.

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