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Comparison of automated home-cage monitoring systems: Emphasis on feeding behaviour, activity and spatial learning following pharmacological interventions

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HIGHLIGHTS

- We compared three automated home cage monitoring systems.
- We determined the effect of pharmacological intervention and strain on behaviours.
- Drug induced changes in the behaviours were established with all three systems.
- Differences between the sensitivity and utility of the systems were observed.

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ABSTRACT

Background: Different automated systems have been developed to facilitate long-term and continuous assessment of behaviours including locomotor activity, feeding behaviour and circadian activity.
New method: This study assessed the effectiveness of three different observation systems as methods for determining strain and pharmacological induced differences in locomotor activity, feeding behaviour and spatial learning. The effect of the CB1 antagonist AM251 on feeding behaviour was determined in the PhenoMaster and PhenoTyper. Next, effects of cholinergic (scopolamine) and glutamatergic (Phenylcyclidine, PCP) receptor antagonism and dopaminergic agonism (apomorphine) on activity were assessed in the PhenoTyper and IntelliCage. Finally, the IntelliCage was utilised to determine differences in activity and spatial learning of C57BL/6 and DBA/2 mouse strains following pharmacological intervention.
Results: AM251 induced a suppression of food intake, feeding behaviour and a reduction in body weight in both the PhenoTyper and PhenoMaster. Apomorphine reduced activity in both the PhenoTyper and IntelliCage. Whereas, decreased activity was evident with PCP in the PhenoTyper, but not IntelliCage and Scopolamine induced a trend towards elevated levels of activity in the IntelliCage but not PhenoTyper. Strain differences in activity and spatial learning were also evident, with increased corner visits and drug induced impairments only observed with C57BL/6 mice.
Comparison with existing method: The automated home cage observation systems determined similar drug and strain effects on behaviour to those observed using traditional methods.
Conclusions: All three observation systems reported drug-induced changes in behaviour however, they differ in their application of spatial learning tasks and utilisation of single versus group housed recordings.

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1. Introduction

A number of different home-cage activity systems have been developed in order to assess the overall activity. These systems are automated and enable the establishment of continuous and long-term monitoring of locomotor activity, feeding behaviour and circadian rhythmicity (de Visser et al., 2006; Riedel et al., 2009; Theander-Carrillo et al., 2006; Edelsbrunner et al., 2009) in

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rodents. The setups of these systems differ in that some utilise video-observation to record movement of individual subjects (e.g. PhenoTyper), while others rely on infrared sensors for the detection of horizontal and vertical activity (e.g. PhenoMaster) (Edelsbrunner et al., 2009). Different again is the monitoring and registration of activity of micro-chipped animals via antenna-containing tubes for entry into activity corners (e.g. IntelliCage; Krackow et al., 2010; Galsworthy et al., 2005). All systems have in common the handling-free assessment of circadian/ultradian activity of rodents (rats, but more frequently mice) for long periods such as weeks or months. However, numerous differences exist which may limit their utility for behavioural testing/learning and this study was conducted with the view to identifying such limitations with respect to drug testing.

Since our laboratory contains all three behavioural observation systems, a series of experiments were performed to highlight differences (advantages, disadvantages) between PhenoTyper (Noldus IT) and PhenoMaster (TSE Systems) in mice. The PhenoTyper consists of clear Perspex walls providing about 0.12 m^2 floor space with front panels allowing access to food and water, which in its most basic version is not automatically monitored. Instead, surrogate measures can be developed to estimate food or water intake as a correlate of time spent in a video-registered water or food zone adjacent to the hopper and bottle (Riedel et al., 2009; Robinson et al., 2013). An infrared camera in the lid monitors the subject's movement in the horizontal plane and a small shelter may be provided in the corner. Resolution of the camera does not support continuous tracking of multiple animals. A similar single-housing solution is the PhenoMaster which consists of a flexible metal frame with infrared beams in both *X* and *Z* axes at 2 levels in height. Adjustments enable high flexibility in terms of floor space for animals in Macrolon home cages of sizes 1–3. Water and food are provided through tethered holders connected to a weight transducer for automatic registration of water and food intake and time-stamping of events. Since animals can remain in their home cage, no habituation periods need to be applied but unobstructed viewing is required for infrared beam brakes; this precludes use of a shelter or environmental enrichment. Since we have already directly compared the two systems using genetically altered mice for basic circadian rhythms (Robinson et al., 2013), we here concentrated on a comparison of recordings of the effects of the cannabinoid receptor antagonist AM251 on food/water intake and activity (Exp. 1). Cannabinoid CB1 receptors have been reported to mediate the regulation of appetite and feeding orientated behaviour, with endogenous cannabinoids and CB1 receptors located in the hypothalamus and other brain regions associated with reward and feeding (Wittman et al., 2007). Previous studies have revealed that CB1 agonists induce hyperphagia in both humans and rodents (Koch, 2001; Hart et al., 2002; Williams and Kirkham, 2002a) with CB1 antagonists reversing the effects of the CB1 agonists (Williams and Kirkham, 2002b; Jarrett et al., 2005, 2007). Acute or chronic administration of the CB1 antagonists SR141716A, AM281 and AM251 alone can induce a reduction in weight, suppress food intake and feeding orientated behaviour (Rowland et al., 2001; Vickers et al., 2003; Riedel et al., 2009) without effects on locomotor activity (Verty et al., 2004; Wiley et al., 2005; Gardner and Mallet, 2006).

Considerable variability to the above systems is provided by the IntelliCage (NewBehavior, now TSE Systems), which registers the subject's activity as an entry into an 'activity corner' through microchip-reading antennae in the access tubes. Typically, a large number (up to 16) of mice can be housed in a central compartment with free access to food. Therefore, food intake cannot be determined for an individual. However, water is only available in the activity corners, with entry into the corners providing a surrogate read-out for general activity. Group housing however does prevent the utilising of male subjects of some mouse lines. We have previously tried to introduce a well accustomed cohort of males from their home cages but ran into difficulties due to the development of new hierarchies between dominant and subordinate mice. Furthermore, the system proved of limited use for ageing and movement disorder studies as drinking requires a strong head tilt of the mouse to reach the vertical bottle spout and the ability to climb through a narrow diameter tube into the corners. Intriguingly, the activity corners are equipped with retractable levers, house lights and the bottles which can be utilised so that simple learning experiments (conditioning, spatial learning) can be conducted in this home cage.

The cholinergic muscarinic antagonist scopolamine is generally found to increase locomotor activity (Chintoh et al., 2003; Nomura et al., 1994; Sipos et al., 1999); with evidence that cholinergic signalling in the hippocampus, striatum and frontal cortex is positively correlated with scopolamine-induced hyperactivity (Day et al., 1991). In contrast, studies with scopolamine in operant/memory based tasks have identified either decreased locomotor activity (Bartholomew Hodges et al., 2009; Masuoka et al., 2006) or no effect (Humby et al., 1999). In addition to effects on activity the blockade of muscarinic receptors with the non-specific antagonists scopolamine or atropine prior to learning has been consistently reported to impair spatial learning and memory in both rats and mice (see Deiana et al., 2011; Klinkenberg and Blokland, 2010 for reviews).

Studies with rodents have revealed that treatment with dopaminergic agonists decrease dopamine synthesis and the firing rate of dopamine neurons which in turn reduces motor function (Spooren et al., 1998; Bunney et al., 1973; Strombom, 1976). These effects are suggested to be mediated by D2-autoreceptors and have been reported for low doses of D2 agonists including apomorphine, 7-OHDPAT and quinpirole (Aghajanian and Bunney, 1973; Missale et al., 1998). They decrease both spontaneous and stimulus induced activity (Di Chiara et al., 1977; Carey et al., 2004), but apomorphine at higher doses increased locomotor activity (Carrera et al., 2012; Matsumoto et al., 1990), induced stereotypy (Battisti et al., 1999), rearing/grooming (Matsumoto et al., 1990, 1991) and cage-climbing behaviours (Marcais et al., 1978; Wilcox et al., 1980). In addition, site directed infusion of apomorphine into CA1 subregion of the hippocampus is reported to induce deficits in spatial memory (Vago and Kesner, 2008; Vago et al., 2007).

Evidence suggests that glutamatergic N-methyl-D-aspartate (NMDA) receptors are involved in the pathogenesis of schizophrenia. Administration of NMDA antagonists including phencyclidine (PCP) and ketamine induce cognitive deficits and both positive and negative symptoms associated with schizophrenia (Jentsch and Roth, 1999) suggesting that hypofunction of NMDA receptors are involved in the aetiology of schizophrenia (Olney et al., 1999). Deficiencies in sensorimotor gating have been observed in both schizophrenic patients (Braff and Geyer, 1990) and in animals treated with NMDA receptor antagonists (Geyer et al., 2001). Low doses of PCP and other NMDA receptor antagonists heightened locomotor activity (Sturgeon et al., 1979; Morita et al., 2000; Bakshi et al., 1999). In addition to effects on activity acute or chronic administration of the NMDA antagonists MK801 (Kesslak et al., 2003; Ahlander et al., 1999), APV-5 (Butcher et al., 1990) and PCP (Beraki et al., 2009; Jentsch et al., 1997; Mandillo et al., 2003) impaired spatial learning and memory.

It has previously been reported that inbred mouse strains display natural differences in a wide variety of behavioural traits (see Crawley et al., 1997 for review). Mouse strain such as C57BL/6 and DBA/2are dissociated based on consistently higher levels of locomotor activity and low anxiety in the open-field in C57BL/6 (Crabbe, 1986; Trullas and Skolnick, 1993; Crawley and Davis, 1982), but these observations have not always been repeated (Trullas and Skolnick, 1993; Podhorna and Brown, 2002). A more

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