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Automated touch screen device for recording complex rodent behaviors

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Abstract

Background—Monitoring mouse behavior is a critical step in the development of modern pharmacotherapies.

New Method—Here we describe the application of a novel method that utilizes a touch display computer (tablet) and software to detect, record, and report fine motor behaviors. A consumer-grade tablet device is placed in the bottom of a specially made acrylic cage allowing the animal to walk on the device (MouseTrapp). We describe its application in open field (for general locomotor studies) which measures step lengths and velocity. The device can perform light-dark (anxiety) tests by illuminating half of the screen and keeping the other half darkened. A divider is built into the lid of the device allowing the animal free access to either side.

Results—Treating mice with amphetamine and the delta opioid peptide receptor agonist SNC80 stimulated locomotor activity on the device. Amphetamine increased step velocity but not step length during its peak effect (40–70 min after treatment), thus indicating detection of subtle amphetamine-induced effects. Animals showed a preference (74% of time spent) for the darkened half compared to the illuminated side.

Comparison with Existing Method—Animals were videotaped within the chamber to compare quadrant crosses to detected motion on the device. The slope, duration and magnitude of quadrant crosses tightly correlated with overall locomotor activity as detected by Mousetrapp.

Conclusions—We suggest that modern touch display devices such as MouseTrapp will be an important step toward automation of behavioral analyses for characterizing phenotypes and drug effects.

Keywords

behavior; mouse; light-dark box; movement; anxiety; motor function; technology; open field

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Introduction

Much of the knowledge gained in the neurosciences has been extrapolated from measurements of animal behaviors responding to surgical, pharmacological and environment/cue-related manipulations. The development of novel neurological and psychiatric pharmacotherapies depends heavily upon how animals respond to these agents in a preclinical setting. Therefore, it is critical to develop methods to quantify animal behaviors in greater detail to characterize potential treatments. In particular, the mouse has become the preferred neuroscience research subject because of the large number of genetic variants that have been developed by laboratories worldwide. Indeed a number of mouse models have been developed for diseases such as Parkinson's disease (PD), Alzheimer's disease, depression/anxiety, and others in order to mimic the genetic, motor and cognitive components of these diseases (Zimprich et al., 2004, Westerman et al., 2002, Cryan and Mombereau, 2004). Therefore, investigating behavioral phenotypes remains an important aspect to characterizing the effects of pharmacological and genetic manipulations.

Behavioral studies have been particularly valuable for the development of novel targets for movement disorders like PD. In PD, a loss of dopamine tone in the brain causes a cascade of neurochemical deficits resulting in a loss of movement. In addition to a generalized loss of movement (akinesia), postural and gait disturbances are also observed clinically. In rodents, gait and postural deficits are more challenging to quantify than generalized locomotion since individual steps must be observed from underneath the animal's body. One way to do these types of experiments is to apply paint to the bottom of the animal's paws and then measure distances and geometries between steps (Fernagut et al., 2002). Other more sophisticated techniques have been used such as the CatWalk XT™ system from Noldus Information Technology. Although these techniques are very useful, each has some drawbacks. Applying paint to animal paws for step measurements does not allow the animal to normally habituate to an environment since paint must be continually reapplied which can cause stress. On the other hand, cost is a significant factor when using commercially available digital imaging analysis systems.

Modern computer and touch display technologies may be useful for exploring new experimental rodent behavior paradigms. Capacitance touch screens work by coating glass with a transparent conductor such as indium tin oxide. The conductance generated by the touch of a human finger or an animal's paw will distort the electric field on the screen and generate a change in capacitance. When coupled to a computing device (i.e. a tablet) a number of applications can be devised. This technology is particularly amenable to animal behavioral studies since it requires no direct pressure to generate a digital signal. In addition, the broad availability of such devices like iPad™ or Android™ tablets use this type of technology allowing for extremely sensitive and accessible touch detection systems.

Here we describe a method in which a consumer grade tablet device is transformed into a complete rodent behavior tracking apparatus. The device (MouseTrapp) is capable of directly recording and scoring animal movements made on the device through a novel software interface. This allows users to then more readily capture behavioral phenotypes in

an automated environment with less user input. Although the device has been used for studying a number of parameters such as novel object recognition (cognition) and gait analysis, the current article describes its application in open field (locomotor activity) and light-dark (anxiety) tests.

Materials and Methods

Hardware

An acrylic chamber was designed with a slot to house a tablet device, leaving only the touch screen portion of the tablet exposed (Fig 1). Dimensions of the apparatus are 21cm (l) × 14cm (w) × 15cm (h). A clear lid was used when performing general locomotor assays while a lid with an opaque top and separation wall is placed within the enclosure for the light-dark test. This separating wall has a 32mm^2 cutout at the bottom to allow a mouse to pass back and forth between each side of the tablet device (Fig 1). An Android (Google, Moutainview, CA) Samsung Galaxy Tab II 10.1 (Samsung, Suwon, South Korea) running a copy of the MouseTrapp software (Neurolytical, Ann Arbor, MI) slides into the opening at the bottom of the chamber. This tablet has a 10.1” diagonal screen which leaves enough room for an adult mouse to ambulate comfortably.

Software

MouseTrapp software was especially designed to detect all “touches” on the screen at any given point and to report these values through a simplified interface. Each mouse paw touching the tablet is therefore registered in the software as an X-Y coordinate. The calculated center of the mouse depends on how many paws are touching the screen. It is assumed that there will be at least two, but no more than four touches at a given time. If there are two or four touches on the screen, a simple average of the points is given as the center position. If there are three touches on the screen, a simple triangular logarithm calculates the precise center of these points, generating a unique X-Y coordinate. These coordinates are continually recorded to track the animal’s movement over time. In addition, a more comprehensive data set is generated detailing all steps made. Therefore, the distances between all steps can be tallied over time as well as the calculated duration of these steps. Velocity of steps is then calculated as length of step/duration of the step. The software then reports all of these data in a .csv (comma separated values) file which can then be transferred to Microsoft Excel^{TM} software for further analyses. It must be noted that mice did not ordinarily drag their tails on the tablet screen during this study, however, when there were occasional touches of the screen by the tail, a touch point was rarely registered. This may be due to the fact that the tails are coated by a thin layer of hair which may prevent the capacitive interaction with the screen that normally occurs with the animal’s paw pads.

Subjects

Male and female C57BL/6J mice (15–30g), obtained from Harlan Laboratories (Indianapolis, IN) or bred in-house, were housed in groups of two to four animals per cage. Animals were between 10 and 15 weeks of age at time of experiment. Mice had free access to standard lab chow and water and were maintained in a temperature- and humidity-

controlled environment on a 12-h dark/light cycle with lights on at 7:00 AM. All animal use procedures complied with the *Guide for the Care and Use of Laboratory Animals* by the National Institutes of Health, and were approved by the *University of Michigan Committee on the Use and Care of Animals*. In total, 35 mice were used. 29 mice were used in the locomotor activity assay with 5–7 animals per drug treatment group. 6 mice were used for the light-dark test.

Drugs

All drugs were administered i.p. and injected at a volume of 10ml/kg. Amphetamine (National Institute on Drug Abuse, Bethesda, MD) was dissolved in saline. SNC80 ((+)-4-[(a-R)-a-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide) was dissolved in 3%HCl and diluted in sterile water.

Apparatus

A Samsung Galaxy Tab®2 running MouseTrapp was inserted into the bottom of a plastic rectangular chamber (for dimensions see *Hardware* section above) and covered with a clear plastic lid. In order to validate the movement recorded by the device, a tripod with a Sony HDR-CX220 digital camcorder was set up to record behavior from above the chamber. For light-dark box experiments, an opaque plastic lid was fitted to the top of the chamber. A panel extended down from the lid to divide the tablet into equal halves. A 3.2^2cm doorway allowed free access between the light and dark sides of the tablet.

For all experiments, the following parameters were used under the “settings” menu of MouseTrapp: Dot Size(px): 20, Touch Color (HEX): 8069A2CA, Center Color (HEX): 8023F08A, Pause Time (ms): 999999999, Movement Threshold (in): 0.1, Time Interval (sec): 30, Show Touches was not checked. For locomotor activity assays, the brightness of the tablet was set to 0. For light-dark box experiments, mice were assayed at brightness settings of ~ 60%.

Locomotor Activity Assay

All locomotor activity assays were run using the “Regular (Black)” mode on MouseTrapp. All animals experienced a 1 hr habituation period in the MouseTrapp apparatus each day for two days prior to the test day. Animals were given a saline injection i.p., placed on the tablet surface, and allowed to explore the chamber freely. The program was activated immediately before placing the animal on the tablet surface. After the habituation (1 hr), another saline injection was administered and the mouse was returned to its home cage. This procedure was repeated on the second habituation day.

On the test day, each mouse was given a saline injection and placed on the tablet for 30 minutes. After the 30 minute habituation, a dose of amphetamine, SNC80, or vehicle was administered i.p. and the mouse was placed on the tablet for an additional 2 hours.

Light-Dark Box

All light-dark box assays were run using the “Light and Dark” mode on MouseTrapp, in which half of the tablet was white and half was black. After activating the program, a mouse was placed on the tablet surface and the chamber was covered with an opaque lid (see “Apparatus”). Fifty percent of the mice started on the dark side and 50% started on the light side. Mice were allowed to explore the chamber for 20 minutes before being returned to their home cage.

Data Analysis

For locomotor activity assays, distance and touch counts were summed over 15 min intervals using the interval data file generated by MouseTrapp. Quadrant cross data was generated by video observation by scorers blind to the drug treatment; a quadrant cross was defined as all four paws of the animal entering a new region. Data were averaged (± standard error of the mean (SEM)) for all mice within a treatment group (N=5–7/group). Statistical analyses were performed on the locomotor activity over time using a repeated measures two-way analysis of variance (RM ANOVA) with a Bonferroni post hoc test where time and treatment were considered independent variables (GraphPad Prism Software, GraphPad Software Inc., San Diego, CA). Locomotor activity for amphetamine or SNC80 graphs on each habituation day were compared by repeated measures (RM) two-way ANOVA (drug treatment X time). If there was no main effect of drug treatment, habituation data were combined across all treatment groups. For all tests, significance was set at $p = 0.05$.

Step distance and velocity data were taken from the “movement_data” file generated by MouseTrapp. Values from the baseline and post drug treatment periods were averaged and plotted separately. For peak activity changes, the step distance and velocity data generated only during the period 40 to 70 minutes post drug treatment were averaged and the baseline was subtracted from this value.

XY position data were taken from the “movement_data” file generated by MouseTrapp. Values were graphed as a scatter plot and adjacent time points were connected.

For light-dark box experiments, total time spent on each side and total touches made on each side were automatically calculated by MouseTrapp and accessed through the “side_count” data file. Data were graphed as mean percent time spent (± SEM) on each side and mean total touches on each side. Statistical analyses were performed using the unpaired t-test.

Results

Amphetamine induced changes in locomotor activity and gait

The first experiment we performed aimed to validate the generalized locomotor activity assay in MouseTrapp. Although MouseTrapp is capable recording and reporting movement data at millisecond (ms) resolution, distance traveled and touches data were binned to 15 min intervals for ease of comparison to quadrant crossing data. Animals were allowed to habituate to the novel environment (i.e. within the MouseTrapp chamber) for two 1 hr sessions prior to treatments. During the habituation periods, there were no significant

differences in locomotor activity between the groups that received 3.2mg/kg AMPH or saline on the test day so the habituation data for the drug and vehicle treated groups were combined. Habituation period shows an overall decrease in locomotor activity as measured by declining distanced traveled (Fig 2a), number of touches made (Fig. 2c) and quadrant crosses (Fig. 2e) within each habituation session and across days (habituation 1 vs 2). Animals were then treated with either saline, 1, or 3.2 mg/kg i.p. amphetamine and then returned to MouseTrapp for data collection. Amphetamine 3.2 mg/kg i.p., but not the lower dose significantly increased distance traveled to a maximum of 1622 inches (41 m) in a 15 min period (45 min after treatment). For distance traveled, RM ANOVA revealed a significant effect of time ($F_{8,104}$= 10.08, $p < 0.0001$), treatment ($F_{2,13}$ = 21.45, $p <0.001$), and a time X treatment interaction ($F_{16,104}$ = 9.40, $p < 0.0001$). Amphetamine 3.2 mg/kg, but not 1 mg/kg also increased the number of touches (steps) to a maximum of 2796 touches in a 15 min period (45 min after treatment). For number of registered touches, RM ANOVA revealed a significant effect of time ($F_{8,104}$= 9.850, $p < 0.0001$), treatment ($F_{2,13}$ = 24.47, $p < 0.001$), and a time X treatment interaction ($F_{16,104}$ = 7.35, $p < 0.0001$). As a control, videotaped quadrant crosses were scored off line. Once again, only the 3.2 mg/kg dose of amphetamine was effective and it caused a maximal 234 quadrant crosses in a 15 min period (45 min after treatment). RM ANOVA on those data also revealed a significant effect of time ($F_{8,136}$= 8.905, $p < 0.0001$), treatment ($F_{2,17}$= 9.089, $p = 0.002$), and a time X treatment interaction ($F_{16,136}$= 9.205, $p < 0.0001$).

To determine how amphetamine may change individual step parameters recorded by MouseTrapp, we assessed the differences in step length and step velocity between mice treated with saline or 3.2 mg/kg amphetamine (i.p.). We examined the total touch data before (30 min) and after treatment (2 hrs). These data show that overall, there was no significant change in step length (Fig. 3a) or velocity (Fig. 3b) compared to basal values. Investigating further, we analyzed data from the peak amphetamine effects (i.e. between 40–70 min) and then analyzed the changes in step length and velocity compared to saline treated animals. Although no changes in step length were observed (Fig 3c), amphetamine significantly($t = 2.57$, $p = 0.033$) increased the velocity with which animals made steps during the 40–70 min post treatment period compared to saline treated mice (Fig 3d).

SNC80 induced changes in locomotor activity

To determine if MouseTrapp could detect changes in locomotor behavior induced by other compounds, we tested of the delta opioid receptor agonistSNC80 using the locomotor activity assay. Animals were habituated on the device for two 1 hr sessions which resulted in net decreases in distance traveled (Fig. 4 a) and number of touches registered (Fig. 4c). Mice receiving 3.2mg/kg SNC80 on the test day had significantly higher locomotor activity during the first habituation relative to mice receiving saline but this difference was not observed during the second habituation. Therefore, the habituation data for the drug and vehicle treated groups were combined. SNC80 (3.2 mg/kg i.p.) significantly increased distance traveled to a maximum of 1387 inches (35 m) in a 15 min period (60 min after treatment; Fig. 4b). For distance traveled, RM ANOVA showed only a statistical trend for time ($F_{8,80}$= 1.844, $p = 0.08$), but did reveal an effect of treatment ($F_{1,10}$= 7.539, $p = 0.021$), and a time X treatment interaction ($F_{8,80}$= 4.197, $p = 0.0003$). SNC80 (3.2 mg/kg i.p.) also dramatically

increased the number of steps recorded to a maximum of 2545 steps within a 15 min period (60 min after treatment; Fig. 4d). For number of registered touches, RM ANOVA revealed a significant effect of time ($F_{8,80}$= 2.962, p = 0.0059), treatment ($F_{1,10}$= 8.622, p = 0.0149), and a time X treatment interaction ($F_{8,80}$= 5.549, p <0.0001). Differences in the locomotor profile comparing saline, amphetamine (10 mg/kg i.p.) and SNC-80 (3.2 mg/kg i.p.) treatment in representative mice can be visualized in Fig. 5.

Light-dark box test application

The light-dark box test is a standard way to determine anxiety levels in mice since they have an innate aversion to brightly lit areas (Crawley and Goodwin, 1980). The MouseTrapp variation of this paradigm uses tablet illumination (white screen) and lack of illumination (black screen) and a separation wall to distinguish these 2 regions. Animals were placed in the Mousetrapp running the light-dark assay for 20 min as described above. The number of steps made on the light side was greater, but not statistically different, compared with the dark side (t=2.014, p=0.072) (Fig. 6a). However, animals spent significantly more amount of time in the darkened half (74% of total time) of the device compared with the light half (t = 3.515, p =0.0056).

Discussion

Monitoring animal behavior is a critical step in the development of therapeutics for human diseases. As neuroscience research progresses with more sophisticated tools to probe the function of distinct neural circuitry such as optogenetics, researchers must rely on behavioral outcomes as readouts to such manipulations. Although there are numerous ways to assess motor behavior including videotaping and offline analysis, applying paint on animal paws or using expensive digital video equipment, a more simplified and inexpensive approach may accelerate findings and make behavioral research more feasible for smaller laboratories.

There have been enormous improvements in consumer electronics over the past decade that take advantage of touch display technologies. In particular, capacitive screen technology has emerged as the touch interface of choice on tablets and smart phones because of its ruggedness and sensitivity. We hypothesized that the sensitivity of such a display on a common tablet device would be capable of detecting mouse steps and that these steps could be processed and reported in a meaningful way for understanding and evaluating behavioral changes. We found that mice steps could generate sufficient capacitance on these displays to register touches as distinct XY coordinates. We therefore set out to develop software which could handle the type of data being generated by animal movement on the device and to develop tests which generate insight into activity, movement parameters, and behavioral measures of emotional states.

Importantly, MouseTrapp generates a number of important parameters which may be useful to investigators that goes beyond traditional quadrant crossing or beam-break paradigms. For instance, data can be binned at different frequencies (to the ms level) to establish higher resolution data. This is important because some manipulations such as a drug microinjection or activation of channels with optogenetic stimulations may only elicit changes on the ms to s time scale. The software also tallies step lengths, velocities and tracks the center of

animal's position over time, thus allowing for traces to be generated following the subject's trajectory over time (Fig. 5).

As a proof of concept, we chose to give a systemic treatment of amphetamine which reliably evokes motor activation in mice. Amphetamine works by reversing dopamine transporters and thereby elevating synaptic dopamine concentrations. Amphetamine's actions are complex, and it was recently shown that thalamo-cortical glutamate transmission plays an important role in amphetamine-induced hyperlocomotion (Mabrouk et al., 2013). By setting up a video camera beside the MouseTrapp device, we were able to measure quadrant crossing (a commonly used locomotor activity measure) within the apparatus for comparative purposes. Amphetamine caused exaggerated locomotor responses as anticipated and MouseTrapp was capable of detecting these changes. These data, including the slope of the curve and duration of effects, strongly overlapped with the quadrant crossing data proving the utility of MouseTrapp in monitoring movement in an open arena. Interestingly we also found a correlation between amphetamine treatment and increased step velocity. This is in line with a recent report showing that amphetamine increases the velocity of head movements in rats (Ma et al., 2013). These data suggest that amphetamine does not increase step lengths, nor does it only grossly increase movement (as recorded by distance traveled), but that it appears to specifically affect the quantity and rate at which steps are taken. Probing these subtle differences in motor parameters evoked by exaggerated dopamine levels may offer insight into the basis of normal and pathological movement.

We were also interested in testing the effects of a systemic treatment of a delta opioid peptide (DOP) receptor agonist on locomotor activity using MouseTrapp. Delta opioid peptide (DOP) receptor agonists such as SNC80 stimulate locomotor activity (Broom et al., 2002, Jutkiewicz et al., 2004, 2008; Mabrouk et al., 2008) without increasing dopamine release directly (Longoni et al., 1998). In addition, these compounds have shown promise as antidepressants (Jutkiewicz et al., 2003), and anxiolytics (Perrine et al., 2006) as well as antiparkinsonian agents (Mabrouk et al., 2008). SNC80 (3.2 mg/kg) increased locomotor responses, as measured by distance traveled and number of touches. These findings demonstrate that MouseTrapp reliably measures activity stimulated by compounds with different mechanisms of action, i.e. drugs that do not directly stimulate dopamine release, and can be used for therapeutic evaluation and development. MouseTrapp also allowed us to qualitatively visualize how SNC80 differs from amphetamine in gross motor activation by plotting X-Y movement coordinates (Fig. 5). These data show how amphetamine causes a more gradual yet persistent behavior activating effect compared to SNC80 and how the effect of SNC80 appears to sharply drop off after 75 min. Amphetamine also stimulated activity primarily along the edges of the touch screen until 75–90 min when the behavior becomes more evenly distributed. However, SNC80-stimulated behavior is more evenly distributed than amphetamine-mediated behavior across the touch screen until 75–90 min where the behavior becomes more concentrated in one corner.

Also described here is the utility of the MouseTrapp device for light-dark box testing as a measure of anxiety. Although the current data do not describe the effectiveness of anxiolytics to reverse the preference of darkened compared to illuminated sides of the chamber, they do show a clear preference for the darkened compared to the illuminated side

of the chamber. Future studies will be necessary to demonstrate how anxiolytic drugs affect this profile, however, it can be assumed that once preference for the darkened area is established, as shown here, anxiolytic-treated animals will increase exploratory behaviors and thus increase the percentage of time spent in the light side. It is interesting to note that in the current test, although time spent in the darkened area was significantly higher than the illuminated side, the number of touches that occurred on either side was not different. Therefore, with this device it it will be possible to more thoroughly probe animal movement behavior during anxious or exploratory states by correlating light area entries with stepping data. It must be noted that a majority of conventional studies which report light-dark behavioral studies utilize chambers that are on the order of 40 cm^2 (Bourin and Hascoet, 2003) while the current device is roughly half this size. Our data suggest that the absolute area of the chamber is less significant than the actual light-dark contrast which the animals respond to. Future iterations of MouseTrapp will take advantage of larger touch display devices as they become more available allowing for testing of larger animals such as rats.

Taken together, these set of data demonstrate the utility of this automated mouse behavioral analysis system that has several built-in tests to quantify not only movement parameters like distance traveled and gait, but also cognitive function. We suggest that using such a device to characterize drug treatments or different phenotypes is an important step forward in mouse behavior monitoring. Furthermore the automated nature of this technology should accelerate the discovery of novel for human diseases ranging from depression/anxiety to Parkinson's disease.

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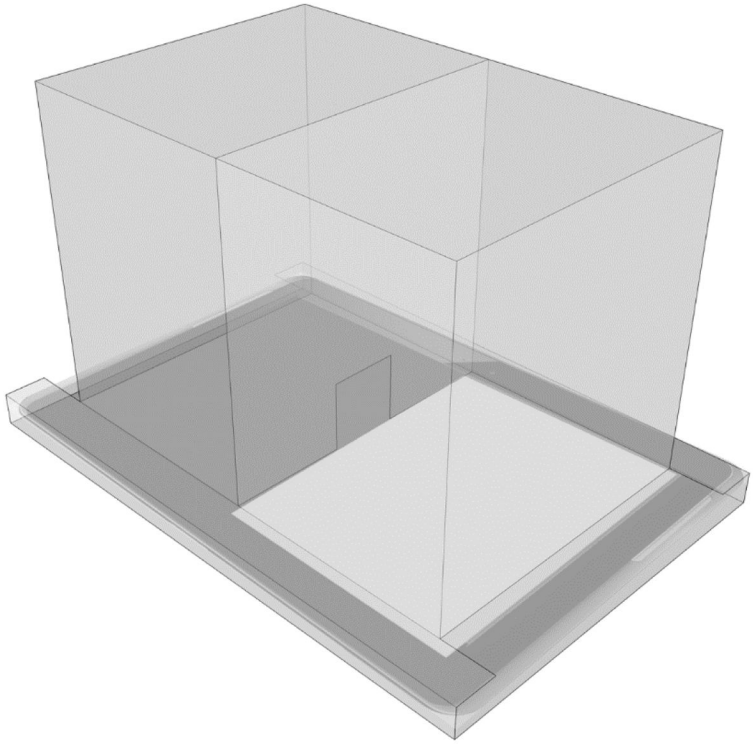

Fig. 1.

A schematic showing MouseTrapp which includes an acrylic enclosure and a slot at the bottom to introduce a tablet device. The configuration shown has a divider, which is attached to the lid, with a small cutout at the bottom allowing free access between sides of the apparatus. The display on the tablet shows lightened and darkened halves which provide the illumination and darkness required for the light-dark test.

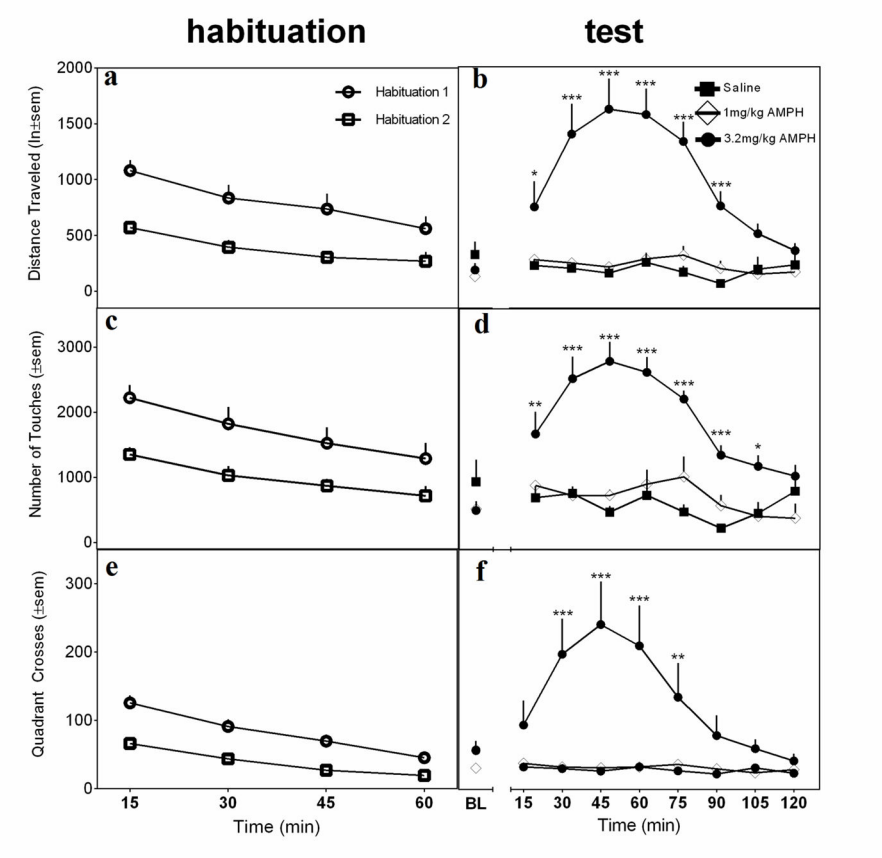

Fig. 2.

Consecutive 1 hr exposures (1 day apart) to MouseTrapp (habituation) cause declining movement scores in terms of distance traveled (a), number of touches (b), and quadrant crosses as measured by video recording (c). Systemic administration of amphetamine (AMPH; 3.2 mg/kg i.p.), but not 1 mg/kg (i.p.) significantly enhanced locomotor activity which was reflected in increased distance traveled (b), number of touches (d) and quadrant crosses (f).

*p<0.05, **p<0.01, ***p<0.001 significance of 3.2 mg/kg i.p. dose of amphetamine compared to saline treatment.

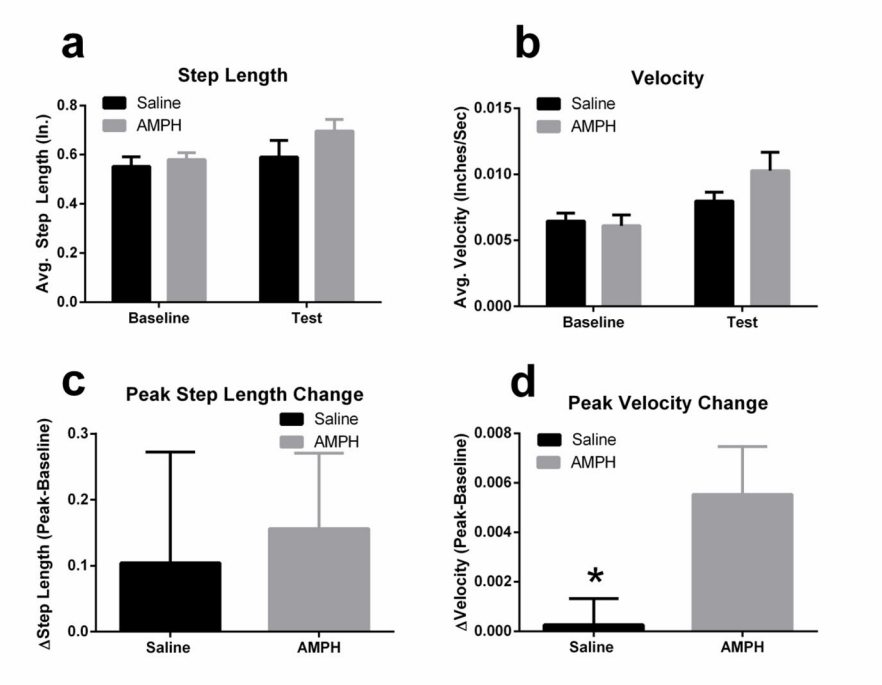

Fig. 3.

Amphetamine (AMPH) 3.2 mg/kg i.p. did not overall change step lengths (a) or velocity of steps (b) as measured by MouseTrapp software when comparing all points prior to treatment and after treatment. When considering only the time points which fell within the maximal effect of AMPH (40–70 min post treatment), a significant increase in step velocity (d), but not length (c) was observed. *$p<0.05$, 3.2 mg/kg i.p. dose of amphetamine compared to saline treatment.

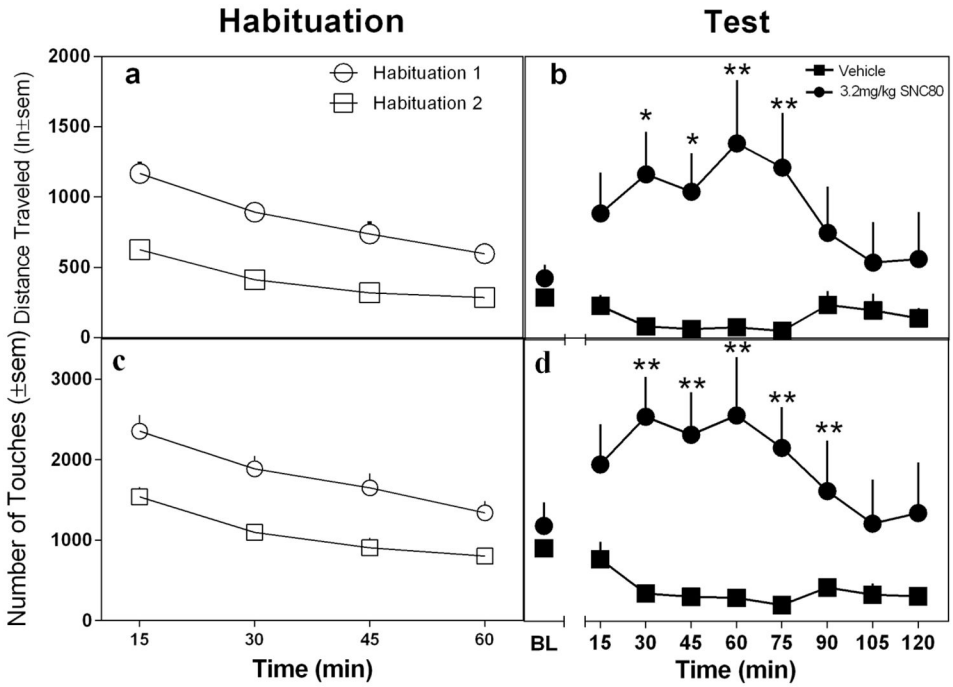

Fig. 4.

Consecutive 1 hr exposures (1 day apart) to MouseTrapp (habituation) cause declining movement scores in terms of distance traveled (a), number of touches (c). SNC-80 3.2 mg/kg i.p. enhanced locomotor activity which was reflected in increased distance traveled (b) and number of touches (d).

*p<0.05, **p<0.01, ***p<0.001 significance of 3.2 mg/kg i.p. dose of amphetamine compared to saline treatment.

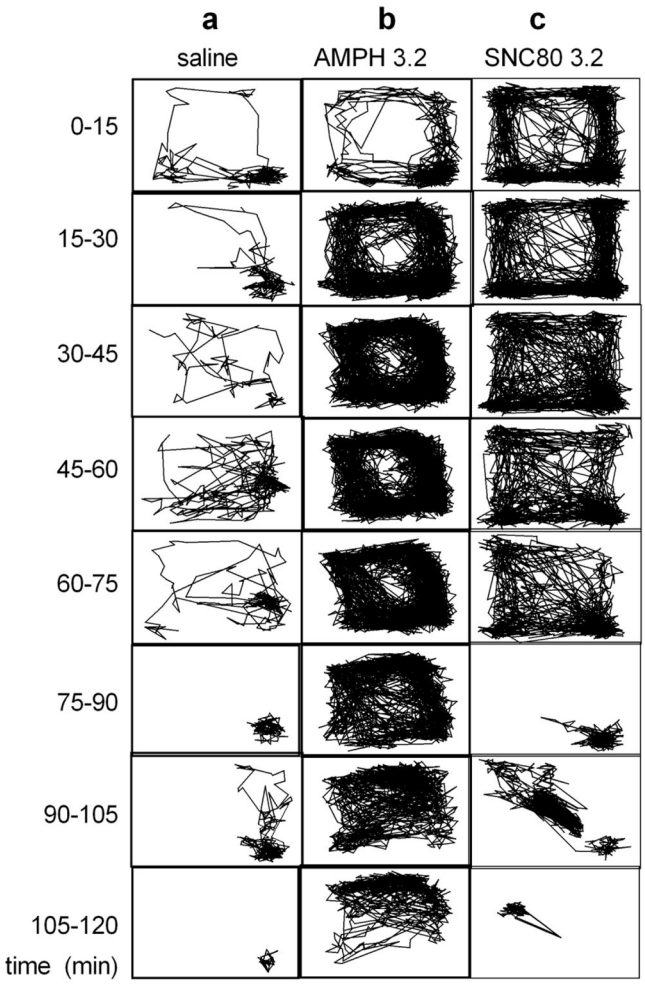

Fig. 5.

Representative traces showing locomotor activity in saline (a), amphetamine (AMPH) 3.2 mg/kg i.p. (b) and SNC80 3.2 mg/kg i.p. (c) treated mice. MouseTrapp generates X-Y coordinates for all animal movement which can then be plotted to determine trajectory, distance and other parameters.

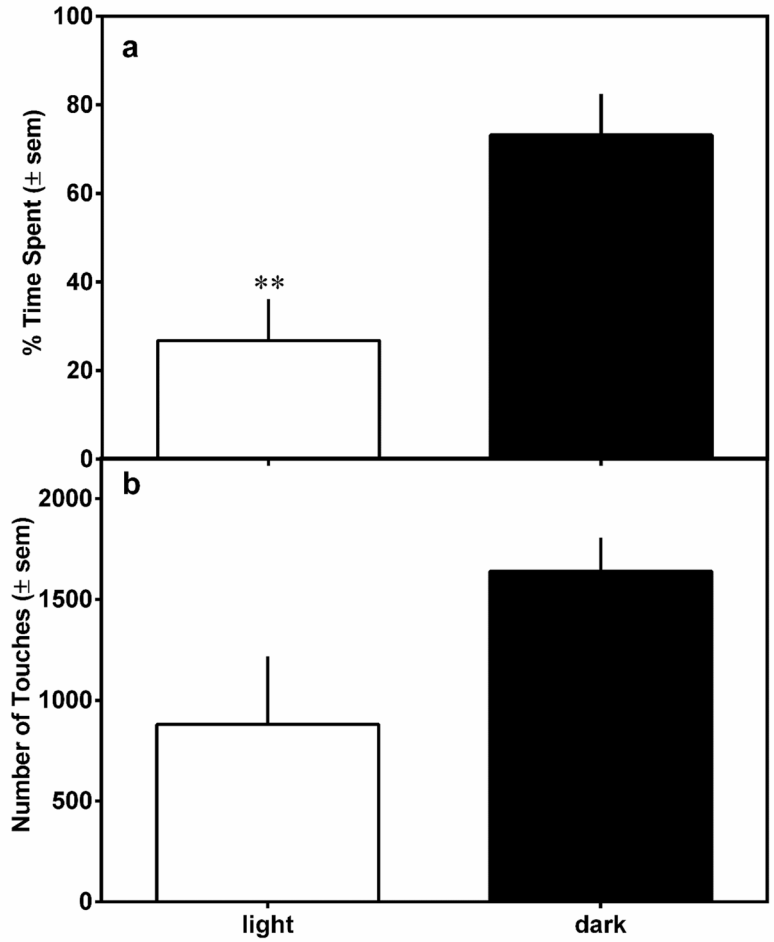

Fig. 6.

MouseTrapp can function as a simple anxiety test in mice by using the touch screen display as a source of illumination. One half of the device can be darkened and then a divider lid can separate these 2 halves. Animals placed in the enclosure (50% started in light and 50% started in dark) have a preference to stay in the darkened part of the arena as indicated by the time spent (a).

*$p<0.05$, significance of time spent in the dark compared to illuminated part of MouseTrapp apparatus during the light-dark test.