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Home-cage activity in heterogeneous stock (HS) mice as a model of baseline activity

J. Mill*, M. J. Galsworthy, J. L. Paya-Cano, F. Sluyter, L. C. Schalkwyk, R. Plomin and P. Asherson

Social, Genetic, and Developmental Psychiatric Research Centre, Institute of Psychiatry, King's College London. UK.
**Corresponding author: J. Mill, SGDP Research Centre, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, SE5 8AF. E-mail: j.mill@iop.kcl.ac.uk*

Behavioral genetic work in humans indicates that clinical hyperactivity is best viewed as the extreme end of activity levels in the population. However, current animal models of hyperactivity are not studied as quantitative traits as they are either knockout models or inbred strains. Furthermore, these animal models generally demonstrate elevated locomotion in novel environments, but not in their home-cages. This is the opposite of the symptoms seen in the human condition where childhood hyperactivity is generally more pronounced in constant, unstimulating situations. In this study we filmed an outbred population of 44 heterogeneous stock (HS) mice under red light during their active phase, to assess the reliability of individual differences in home-cage behavior and extract an index of home-cage activity (HCA) level. We then compared this measure to locomotor behavior in a novel environment –– the open-field. Reliable individual differences in home-cage behaviors such as running, swinging on bars, and burrowing were found, and principal component factor analysis yielded a general activity factor, which accounted for 32% of the variance and correlated 0.90 with a subjective impression of activity level. The correlation between HCA and locomotor activity in the open-field was 0.23, which was non-significant. However, the association with HCA level appeared to increase over the five minutes of the open-field, presumably as the mice habituated. Furthermore, although mice displaying particularly high and low HCA were indistinguishable early in the open-field task, they became significantly differentiated over time. We conclude that home-cage behaviors and the open-field, after habituation, display good face and construct validity, and may provide a good model of baseline activity for quantitative trait loci (QTL) discovery and functional genomics in the HS mice.

Keywords: Animal models, attention deficit hyperactivity disorder (ADHD), baseline activity, factor analysis, genetics, home-cage activity, HS mice, hyperactivity, open-field activity

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Hyperactivity is a problem in several clinical disorders, perhaps most notably in attention deficit hyperactivity disorder (ADHD), which is also characterised by inattention and impulsivity. ADHD is one of the most prevalent forms of child psychopathology affecting between 2 and 5% of school-age children, with a strong male sex-bias in clinical samples. However, although a disorder such as ADHD is diagnosed using operational criteria to define diagnostic categories, measures of hyperactivity are continuously distributed in the general population and many studies have found an excellent correspondence between quantitative measures of hyperactivity and the categorical diagnosis (Levy *et al*. 1997).

Twin and adoption studies suggest that hyperactivity is highly heritable and familial analyses indicate that it is mediated by the effect of numerous genes of small effect interacting both with the environment and each other. Furthermore, behavioral genetic studies suggest that both ADHD and the underlying quantitative trait of hyperactivity may share the same genetic aetiology (Eaves *et al*. 1997). This conclusion gains some support from the finding that polymorphisms within the dopamine D4 receptor and dopamine transporter genes found to be associated with ADHD (Faraone *et al*. 2001), are also associated with quantitative measures of hyperactivity in some studies (e.g. Curran *et al*. 2001).

The hunt for the genes or quantitative trait loci (QTL) that predispose humans to complex traits, such as hyperactivity, is difficult but is making progress (Asherson & Curran 2001). Mouse models are useful in identifying QTL for complex traits because they provide greater genetic and environmental control (Crabbe, in press) and will be especially valuable for functional genomic research that aims to understand brain mechanisms that mediate genetic effects on behavior. Table 1 lists a few examples of current animal models for hyper-locomotion, which consist of inbred strains, selected lines, genetic knockouts, and transgenic animals. Such models have provided valuable insights into some of the behavioral deficits and pharmacological changes associated with hyper-locomotion in these animals.

However, a major limitation in the use of knockouts is that they do not help in the hunt for novel candidate loci that cause individual differences in traits such as hyperactivity, because they are only one experimental change in otherwise genetically identical animals. Furthermore, typical gene knockouts, which totally eliminate gene function, will often be unrealistic models of QTL, which in many cases act by quantitatively altering levels of gene expression or gene function. In fact, gene deletions often give rise to other non-specific global physical and behavioral effects, and hyper-locomotion itself is a common outcome when knocking-out a whole range of different genes. Similarly, selection studies

Table 1: Examples of animal models of the hyperactive phenotype

Model	Reference(s)	Description
6-hydroxydopamine (6OHDA) lesioned neonatal rat	Shaywitz *et al*. (1976)	60HDA selectively damages catecholaminergic neurons and produces hyperactivity. This model established a role for dopamine and the nucleus accumbens in the expression of hyperactivity.
Spontaneously Hypertensive Rat (SHR)	Sagvolden *et al*. (1992)	Result of selectively inbreeding rats of the Wistar-Kyoto stock that exhibit high systolic blood pressure. Found to be significantly more active in open-field tests than its normotensive strain. Behaviors appear to parallel ADHD-related behaviors – more sensitive to immediate reinforcement and less sensitive to delayed reinforcement.
Coloboma Mouse	Hess (1996)	Extremely hyperactive in open-field tests. Behavior a result of deletion of the SNAP-25 gene, a neuron-specific plasma membrane protein that facilitates synaptic vesicle fusion at the presynaptic membrane.
Acallosal mouse strain I/LnJ	Magara *et al*. (2000)	Defective interhemisphere cross-talk caused by hypoplasia of the corpus callosum. Have behavioral features resembling ADHD – especially hyperactivity and low agoraphobic attitude in open-field tests.
DAT1 Knockout Mouse	Giros *et al*. (1996)	Dopamine transporter gene (DAT1), which has been associated with ADHD, was totally knock-ed-out. This resulted in spontaneous hyper-locomotion in the open-field. Interestingly much of this was overcome with adaptive changes such as decreases in neurotransmitter and receptor levels.

are far from perfect models in which to find QTL, as alleles not affecting the trait under investigation can easily be fixed during selection. The best strategy for finding new QTL is to open up the variance again by interbreeding high and low activity animals and to track genes via a linkage design. Variants of such an approach are already in use in the hunt for QTL. Flint *et al*. (1995), for example, found several QTL for open-field activity in an F2 cross between high and low lines selected for open-field activity. Moisan *et al*. (1996) found the first, and to date only, QTL influencing hyper-locomotion in the rat by selecting divergent animal lines on the basis of their differential activity. However, the resolution of this type of mapping is coarse because the chromosomes of the F2 animals have undergone very little recombination. Much finer resolution QTL mapping in rodents can be achieved by using an outbred stock of animals for which the entire genealogy is known. An example of these are the heterogenous stock (HS) mice, a systematically outbred stock established over 30 years ago from an eight-way cross of C57BL/6, BALB/c, RIII, AKR, DBA/2, I, A/J and C3H inbred mouse strains (McClearn, Wilson & Meredith 1970). As well as vastly increasing the genetic variation amongst the experimental animals, such stocks are also more representative of a general population in terms of behavioral traits, with individual genetic differences mapping onto individual behavioral differences.

The aim of our work is to use this population of HS mice to map QTL influencing activity levels. However, to date, most studies of hyper-locomotion in rodents have focused on overactivity in the open-field. Although several studies have utilised principal component factor analyses to investigate open-field activity and discovered the existence of stable behavioral traits with good measurement validity (e.g. Ossenkopp *et al*. 1994 and Jahkel *et al*. 2000), the purpose of this study was to develop activity measures based on natural variance of baseline activity levels in unstimulating environments, which may better model the condition seen in human hyperactivity. The rationale behind this approach is that most 'overactive' animal models demonstrate normal home-cage activity and only appear overactive in novel environments (e.g. Zhuang *et al*. 2001). Children with ADHD, however, generally show the inverse of this relationship – so that overactivity is more pronounced in certain constant and unstimulating situations than it is in novel situations. This is exemplified by Sagvolden *et al*. (1998) who found that during a long experimental session, activity levels of ADHD boys started off as 'normal' but increased as time progressed. Furthermore, a recent study by Antrop *et al*. (2000) found that children with ADHD were significantly more hyperactive than control children in unstimulating environments, but not in more stimulating situations. Thus, we believe a more realistic hyperactivity animal model would be one that displayed a marked increase in levels of home-cage activity, but less apparent increases in novel-environment activity, compared to 'normal'.

In order to develop behavior tests based on these understandings, we chose to pilot a simple measure of home-cage activity in HS mice and compare this with a standard measure of activity in a novel environment, the open-field. Furthermore, instead of employing wheel-running recording, tracking software or vibration-sensitive platforms to assess home-cage activity, we chose to examine the behaviors that animals perform in the home-cage in order to better understand the reliabilities of these various behaviors and their contributions to measures of activity level. Given the previously mentioned findings of Zhuang *et al*. (2001) and a recent study of Bronikowski *et al*. (2001) in which mice selectively bred for high wheel-running did not differ from control lines

in open-field activity, we hypothesised that home-cage activity and open-field activity would be weakly, if at all associated. Furthermore, we chose to analyse the open-field locomotion minute by minute as we believed any baseline activity levels would be more likely to be masked early in the test by anxiety and activity elicited by novelty.

Materials and Methods

HS mice

As described above, the HS is a systematically outbred stock established over 30 years ago from an eight-way cross of C57BL/6, BALB/c, RIII, AKR, DBA/2, I, A/J and C3H inbred mouse strains (McClearn, Wilson & Meredith 1970). Mice from the 65th generation were obtained from the Institute for Behavioral Genetics at the University of Colorado at Boulder. The pups were weaned at 21 ± 2 days and housed in same-sex groups of up to five per cage. Identification was coded by natural coloration, tail tattoo and ear punch markings (marked on arrival). On arrival in the UK animals were housed individually and maintained in a standard 12-h light/dark cycle (reversed) in an environment controlled for temperature (21 ± 2 °C) and humidity. Food and water were continuously available. Two weeks of acclimatisation were allowed before testing. The age range was 19 days and testing began when the mice were on average 8 weeks old. A total of 44 mice were tested; 22 males and 22 females.

Behavioral assessment – home-cage

The home-cages were 30.5 × 13 × 11 cm, and made from white plastic (see Fig. 1). The removable lid was made from metal wire bars spaced 5 mm apart, with two hoppers 8.5 cm deep at one end – one for food pellets, and the other for a water bottle. The mice were filmed in batches of 8 from above in their home-cages during their dark cycle, which is when they are active. After home-cages were moved to the filming arena, the mice were left to settle for 10 min before filming took place. Mice cannot see red light beyond 630 nm (Jacobs *et al*. 1999), so they were filmed under 660 nm red light (MARL Series 501 LED cluster, RS Components, Corby, USA). Each mouse was filmed for two one-hour periods at different times (10am until 11am and 4 pm until 5 pm) on two consecutive days. Mice are active nocturnally, so on a reversed 12 h cycle their active period occurs during the day. The mice were coded on a range of activity-related behaviors from the video recordings for three five-minute periods in each hour of filming (10 min-15 min, 25 min-30 min and 50 min-55 min).

The following variables were coded:

1 Bar swinging: total time spent hanging or swinging from cage roof bars
2 Floor activity: total time spent active on floor of home-cage (i.e. running)
3 Burrowing: total time spent exhibiting burrowing behavior (in sawdust or nesting material)
4 Feeding/drinking: total time spent obtaining and consuming food and water from reservoirs
5 Stationary/grooming: total time spent outside nest either sedentary or performing grooming behaviors
6 In nest area: total time spent inactive under the food and water hopper

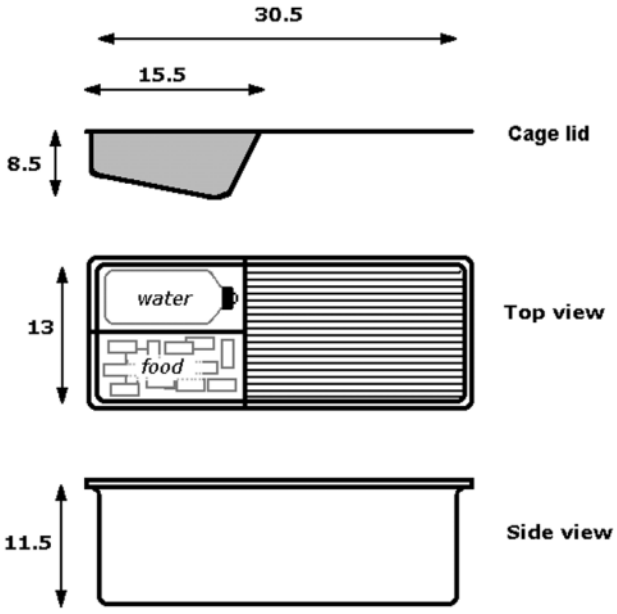

Figure 1: The dimensions of the home-cages. All dimension are in centimetres. Diagram to approximate scale only. The home cages consist of a non-transparent (but not completely opaque) white plastic tray with a metal cage lid. The metal lid has a food and water hopper, and approximately 17 wire bars space 0.5 cm apart.

At the end of each 5 minute session, each mouse was also given a subjective general activity score ranging from 1 (very inactive) to 10 (very active) based on the general impression of activity given by each individual animal over the coding period. This score was determined mainly by how energetically and continuously the animal had appeared to move during the five minute session, and was given blind to previous assessments for the same animal.

Behavioral assessment – novel arena

The open-field is a lidless box with white acrylic walls and floor. Internal dimensions are 72 × 72 × 33 cm and the light level was 150 Lux. Mice were placed in a corner and allowed 5 min to explore the arena while they were videotaped by a camera overhead. For coding from video, the arena was divided into a 4 × 4 grid (each square 18 × 18 cm), and line-crossings (all four paws over a grid-line) were counted for each minute. This provided an index of locomotor activity for minutes 1, 2, 3, 4 and 5 of the open-field. Open-field activity measured in this way was found to correlate 0.98 with a direct measure of distance travelled during the 5 min obtained using the NOLDUS ETHOVISION (version 2.2.14) tracking software on a subset of 35 of these mice (the albinos could not be tracked due to the white background).

Analysis

All analysis of the behavioral data was performed using the computer program STATA (version 6.0, Stata Corporation, College Station, TX, USA). First the means and standard deviations for each home-cage behavior measure were calculated. Reliabilities of these behaviors were then assessed by mean correlations between the six samples, Cronbach's alpha and AM (day 1) – PM (day 2) correlation. Cronbach's alpha measures how well a set of variables measures a single unidimensional latent construct. The samples were then summed to make behavioral scores for 'swinging', 'floor activity', etc. and relationships between these were examined in a correlation matrix. Principal component factor analysis (PCFA) was then employed to derive a first activity component from the six behaviors (not the subjective activity). The principal component from PCFA represents the largest influence on a set of measures by accounting for as much of the variability in the data as possible. PCFA is therefore a data reduction method used to extract the major trait influencing a set of measures. The principal component derived from the six behaviors assessed here was then correlated with the subjective activity score to test the face validity of the HCA construct.

Results

Home-cage descriptive statistics

Table 2 shows the means and standard deviations for time engaged in each of the six coded behavioral variables (measured in seconds) and the subjective activity score at each of

Table 2: Means and standard deviations for the seven measures

Measure	AM (1) Mean (SD)	AM (2) Mean (SD)	AM (3) Mean (SD)	PM (1) Mean (SD)	PM (2) Mean (SD)	PM (3) Mean (SD)	Proportion of time
Bar Swinging	101.2 (50.8)	87.0 (62.9)	89.8 (69.1)	117.0 (71.7)	103.6 (71.0)	76.5 (67.9)	32%
Floor Activity	48.2 (21.2)	27.8 (14.6)	34.7 (22.6)	42.3 (22.2)	29.2 (14.9)	33.8 (21.7)	12%
Burrowing	6.5 (9.9)	4.7 (6.9)	4.2 (7.4)	3.3 (5.0)	2.9 (5.0)	4.5 (7.1)	1%
Feed/Drink	61.2 (47.5)	50.9 (43.7)	54.8 (52.2)	55.7 (60.6)	59.0 (57.0)	70.3 (73.1)	20%
Stationary/Grooming	51.5 (38.0)	81.5 (56.9)	44.3 (38.8)	38.9 (30.4)	64.9 (51.6)	46.1 (36.7)	18%
Nest Area	31.3 (38.9)	48.1 (75.8)	72.2 (101.7)	42.7 (67.9)	40.4 (59.5)	68.9 (89.0)	17%
Subjective Score	6.0 (1.5)	5.3 (1.9)	5.5 (2.3)	6.1 (1.7)	5.6 (1.9)	5.3 (2.0)	N/A

Table 3: Pearson's correlations, Cronbach's alpha, and between-day correlation for each individual measure (* = Ch alpha > 0.60, or $p < 0.05$ for correlation; ** = Ch alpha > 0.80, or $p < 0.01$ for correlation)

Measure	Average intersession correlation	Chronbach's alpha[a]	Day 1 – Day 2 Correlation[b]
Bar Swinging	0.34*	0.75*	0.57**
Floor Activity	0.25	0.66*	0.53**
Burrowing	0.15	0.54	0.36*
Feed/Drink	0.18	0.55	0.30
Stationary/Grooming	0.07	0.19	0.13
Nest Area	0.31*	0.70*	0.40**
Subjective Score	0.48**	0.84**	0.67**

[a]Cronbach's alpha was performed on unstandardised values.

[b]Note that 'Day 1' is the summed three scores for day 1 (all AM) and 'Day 2' is the summed three scores for day 2 (all PM) so that the Day 1 – Day 2 correlation represents reliability across both day and time of day.

Table 4: Correlation of mean standardised scores for each measure

	Swing	Floor Activity	Burrow	Feed	Stationary/ Grooming	Nest	Subjective Score
Swing	1.0						
Floor Activity	0.18	1.0					
Burrow	0.02	0.33*	1.0				
Feed	−0.39**	−0.03	−0.20	1.0			
Stationary/Grooming	−0.18	−0.06	−0.05	0.04	1.0		
Nest	−0.65**	−0.41**	−0.03	−0.29*	−0.25	1.0	
Subjective Score	0.90**	0.43**	0.02	−0.15	−0.09	−0.81**	1.0

(*$P < 0.05$; **$P < 0.01$).

Table 5: Principal component factor analysis for the six timed activity measures.

Activity	Factor loading
Bar Swinging	0.81
Floor Activity	0.66
Burrowing	0.33
Feed/Drink	−0.19
Stationary/Grooming	−0.01
Nest Area	−0.82
Eigenvalue of first factor	1.90
Proportion of variance	32%

Table 6: Correlation between individual Open-field (OF) line-crosses and Home-cage Activity (HCA)

	OF1	OF2	OF3	OF4	OF5	HCA
OF1	1.0					
OF2	0.48*	1.0				
OF3	0.42*	0.80*	1.0			
OF4	0.58*	0.57*	0.58*	1.0		
OF5	0.45*	0.66*	0.72*	0.68*	1.0	
HCA	0.07	0.09	0.26	0.17	0.33*	1.0

*$P < 0.05$.

the six assessment stages (scored between 1 and 10). There were no significant differences between Day 1 (a morning session) and Day 2 (an afternoon session) for any of the six behavior scores or the subjective activity score ($t = 0.19$, $p = 0.85$). There were, however, some changes in behavior over the hour of recording on both days, with session number correlating significantly with bar swinging ($r = -0.16$, $p > 0.01$), floor activity ($r = -0.22$, $p < 0.001$), time in nest ($r = 0.18$, $p < 0.005$) and with the subjective activity score ($r = -0.15$, $p < 0.05$).

Reliabilities of behaviors

Table 3 shows the reliability statistics for the six measures (AM-1, AM-2, AM-3, PM−1, PM-2 and PM-3) of the seven activity variables. Average correlations between the samples were positive for all measures, indicating a certain degree of reliability. However, this was only significant for three of the seven variables. Average correlations ranged from 0.07 to 0.48 with the most internally correlated measures being the subjective activity score (0.48), bar swinging (0.34) and time spent in nest (0.31), and the least internally correlated measure being time spent stationary/grooming (0.07). Cronbach's alpha values were also calculated to indicate the reliability of the individual measures, and values ranged from 0.19 to 0.84, with the most reliable measures being the subjective activity score (0.84), bar swinging (0.75), in nest (0.70), and floor activity (0.67).

Factor analysis across behaviors

The six assessments for each behavior were summed to give the total time spent performing that behavior during the 30 min of coded recording. Similarly, the subjective activity scores were summed to give a total 'subjective activity measure'. The correlations between these total scores from different measures can be seen in Table 4. The strongest associations with the subjective activity rating are time spent bar swinging (0.90) and time spent in nest (−0.81). The strongest correlation amongst the measures is between bar swinging and time in nest (−0.65).

The behaviors in Table 4, excluding the subjective activity rating, were submitted to unrotated principal component factor analysis in order to extract a latent variable that best indexes a general factor accounting for maximal covariance among the measures. The resulting HCA construct has an eigenvalue of 1.90 and explained 32% of the variance. As shown in Table 5, there were strong positive loadings from bar swinging (0.81) and floor activity (0.66), a strong negative loading from time spent in nest (−0.82), a small positive loading from burrowing (0.33), and near-zero loadings from feeding and stationary/grooming behaviors. The pattern of these loadings suggests that this factor represents activity level, a conclusion further validated by correlating the principal component with the subjective activity score. As can be seen in Fig. 2 these two variables correlate highly significantly (0.90), providing further evidence that the principal component represents underlying activity.

Novel arena descriptive statistics

The mean number of line-crosses during the five minutes in the open-field test was 105.5 (SD = 43.4), with a range in the population from 7 line-crosses to 204 line-crosses. Minute by minute, the mean number of line-crosses were: min 1 = 13.8 (SD = 7.5); min 2 = 24.8 (SD = 11.9); min 3 = 21.1 (SD = 11.3); min 4 = 22.7 (SD = 10.8); and min 5 = 23.13 (SD = 10.6). Across each of the five minutes detailed there appears to be a high degree of reliable individual differences in line-crossing, with the five one-minute samples correlating to 0.60 on average, and a Cronbach's alpha (unstandardised) value of 0.88. These correlations (shown in Table 6) appear

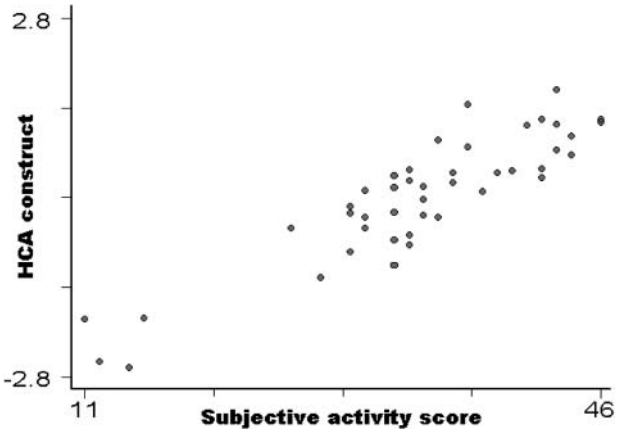

Figure 2: A graph showing the high association between subjective impression of activity level and the Principal Component Factor for the home-cage behaviors.

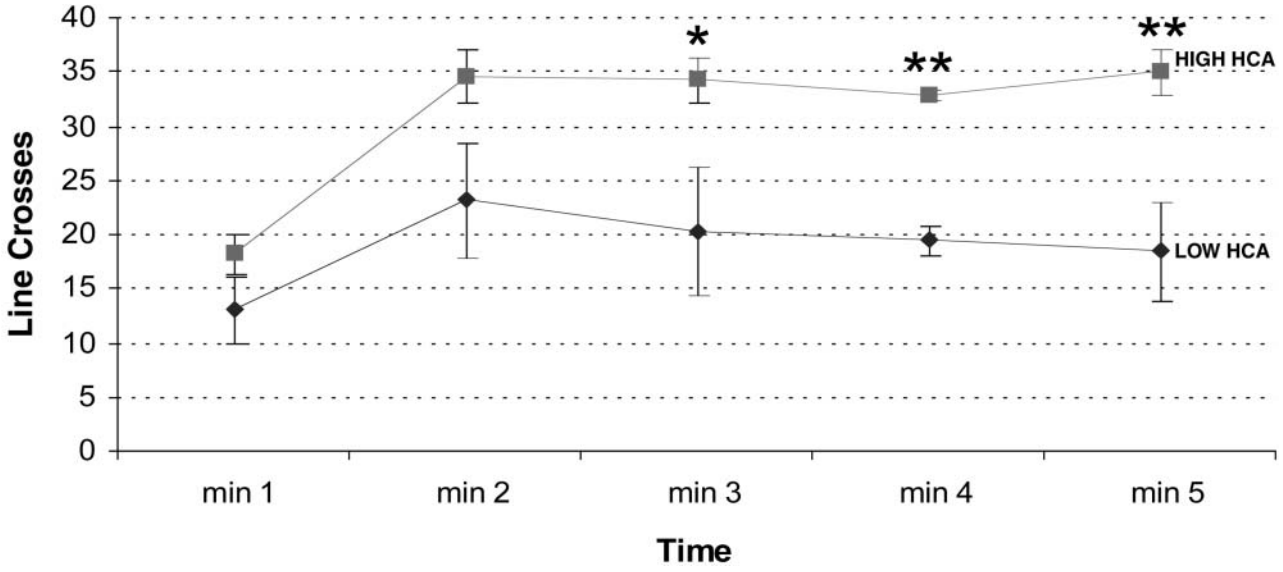

Figure 3: A graph comparing of the five highest and five lowest home-cage activity mice on the open-field (*$P < 0.05$; **$P < 0.01$). Number of line-crosses in the open field over 5 minutes. Bars denote standard error.

to indicate that it is the first minute that has the lowest degree of similarity with other time-periods. This is confirmed by principal component factor analysis and item detail for the Cronbach's alpha, which identified the first minute as having the most unique variance (non-significant difference).

Association between home-cage and novel arena measures

We compared home-cage activity with line-crossing activity in the open-field. The overall correlation was found to be 0.23. However, as shown in Table 6, there is a tendency for

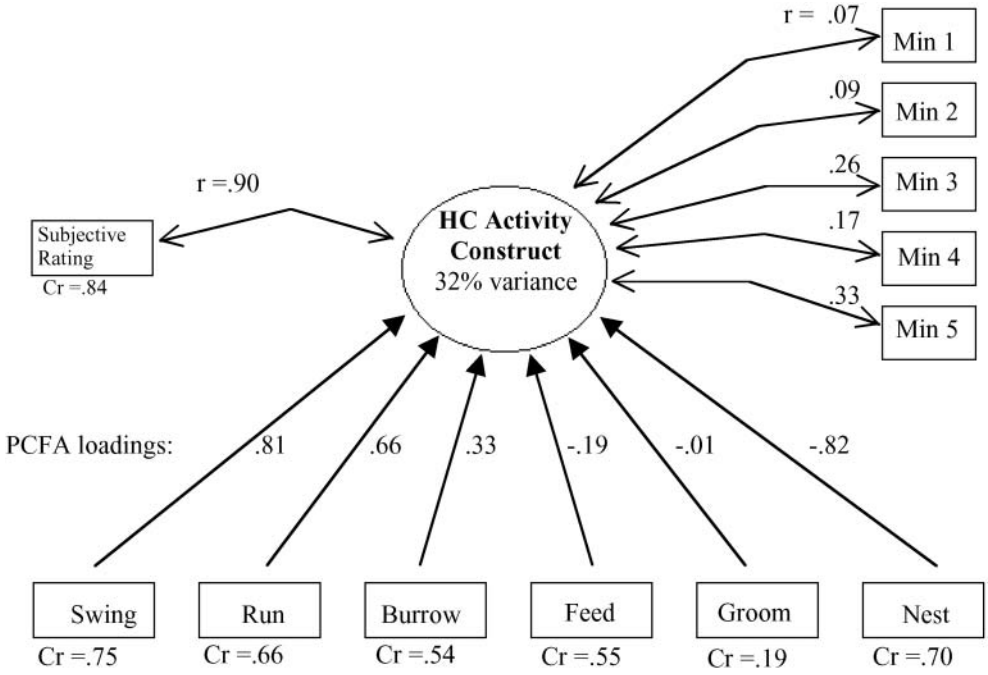

Figure 4: Model summarising the observed relationships between different measures of activity.

higher correlations with the HCA construct as time goes on, possibly because the first few minutes of the OF task have a larger anxiety factor. Figure 3 compares the five highest and five lowest HCA mice on the open-field. It can be seen that there is no significant difference for the first 2 min, then a significant difference in the third, and a highly significant difference in the 4th and 5th minutes.

Discussion

Our data demonstrate reliable individual differences in home-cage activity-related behaviors, and furthermore provide evidence that a realistic and informative index of activity can be taken from such measures. The data strongly suggest that most home-cage behaviors are internally consistent, with Cronbach alpha's scores from six five-minute samples in the range of moderate to good for all but the stationary/grooming measure. Principal component factor analysis (PCFA) to extract an overall activity variable suggested that it was swinging behavior, running, and nesting that load most strongly onto this activity factor that accounts for 32% of the variance. Analysis shows that these are also the three most reliable measures, together accounting for 64% of the total time in the six five-minute assessment periods. The subjective activity measure appears to be highly consistent and, as might be expected, correlates strongly with swinging behavior (positive), running (positive) and nesting (negative). Figure 2 demonstrates how this subjective activity measure also correlates highly significantly with the activity factor extracted by PCFA (0.90), indicating the face validity of this statistically extracted variable.

Finally, the HCA data were also analysed in relation to activity in the open-field. Stable individual differences in locomotor activity were seen across the five minutes of assessment, and these appeared to become more associated with the home-cage (baseline) activity level as time progressed (Table 6). This was paralleled by results for the five highest and five lowest HCA mice which became significantly differentiated in open-field locomotor activity only after the first two minutes, as shown in Fig. 3. It is possible that the initial open-field response is one of anxiety and/or some excitement in response to the novel situation, which could effectively mask individual differences in baseline activity level. It also appears as though the high HCA mice do not begin to habituate after reaching their maximum locomotor activity levels in the open-field (see Fig. 3) – however, this would be best tested by a replication using a longer open-field assessment. An overall summary of the data obtained in this study can be seen in Fig. 4.

The reliability of this home-cage activity construct would most probably improve if longer sampling frames were used as indicated by increased mean correlations between summed Day 1 samples with summed Day 2 samples (see Table 3). A potential confound in the associations of behavior presented, however, is that the home-cage measures are not entirely independent as they are all competing for the same time. Furthermore, the mice appear to be more active (scoring higher on bar swinging, floor activity, and the activity rating, and lower on nest area time) in the first five-minute assessment period (AM1/PM1) of each session than the last five-minute assessment period (AM3/PM3). This suggests that the animals may still be restless after their cages have been moved into the assessment arena, and in subsequent experiments we intend to expand the habituation time.

The factor analytic method utilised in our study may too lengthy and complicated for some study designs, especially as it is only suitable to individual differences research. Its importance lies in demonstrating the construct validity of this approach and in identifying simpler measures of activity such as subjective rating or open-field activity after a period of habituation. Further work will aim to develop a more refined battery of home-cage activity measures that still accurately assess the statistically stable behavioral differences found in our pilot data.

An interesting follow-up to these results would be to further explore how activity changes in a new arena as mice habituate to it. Relative to other mice, the 'ADHD mouse' would be predicted to show high HCA, normal initial response to the novel situation and rapid return to high activity as it gets 'bored'. It might also be the case that the complexity or interest level of the novel arena is a factor in the rate at which high and low hyperactivity mice differentiate – with low complexity/interest allowing the more rapid differentiation. Additionally, the human literature would predict that introducing novelty to a habituated environment would render high baseline activity mice and low baseline activity mice less distinguishable. Finally, our ongoing work aims to explore the association of activity levels with behavioral aspects that tend to be associated in humans, such as attention and impulsivity. We hope this work will result in a more naturalistic model of hyperactivity with better behavioral validation than other animal models have provided to date. We also hope that these efforts to better understand and measure baseline activity differences will provide a useful basis for QTL discovery and functional genomics exploration of hyperactivity.

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