The IntelliCage as high-throughput behavioral screening tool: spontaneous behavioral profiles of strains, brain lesions and mutants

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University of Zurich[UZH] | ETH Eidgenössische Technische Hochschule Zürich Swiss Federal Institute of Technology Zurich

ZNZ Zentrum für Neurowissenschaften Zürich Neuroscience Center Zurich

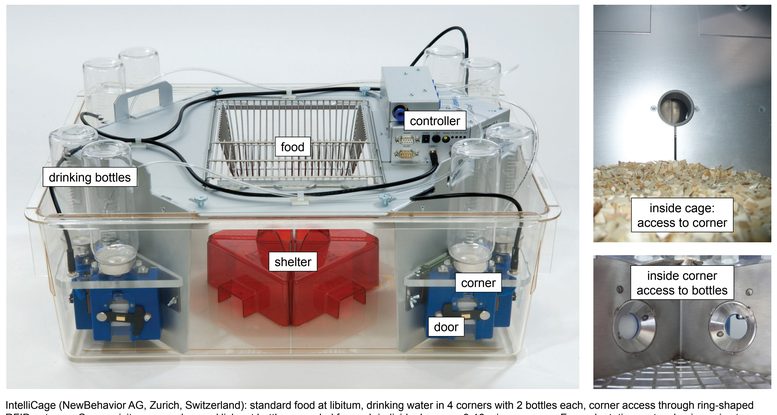
ZIHP Neural Plasticity and Repair National Center of Competence in Research

Introduction

Traditional behavioral tests for mice are inefficient. They involve isolation, exposure to unfamiliar apparatus, and repeated handling. Resulting stress responses introduce artifacts and make testing unreliable. Automated assessment of behavior in the homecage may eliminate many of these problems. The IntelliCage collects individual data from socially housed RFID tagged mice and thus also eliminates isolation stress and enables parallel testing of large numbers of mice. While many specialized protocols have been developed for IntelliCage to test learning and memory, attention, impulsivity and emotional responses, all mice begin testing with some days of free adaptation. Spontaneous corner visits, nosepoking patterns and licking activity are already monitored 24/24h during this phase.

The aim of this study was to use these data to establish profiles of spontaneous behavior in IntelliCage that allow to distinguish mouse strains and various brain lesions and can be used as reference for the pre-screening of new mutant lines.

Methods



IntelliCage (NewBehavior AG, Zurich, Switzerland): standard food at libitum, drinking water in 4 corners with 2 bottles each, corner access through ring-shaped RFID antenna. Corner visits, nose pokes and licks at bottles recorded for each individual mouse. 8-16 mice per cage. Free adaptation protocol: mice naive to cage, 7 days all bottles freely accessible 24/7, dark phase 8-20h. Brain lesions: C57BL/6J, NMDA injection (hippocampus, prefrontal cortex, dorsolateral striatum), conditional mutations (habenula, dorsal cortex). Mutants: APP-DM = APPsa-KI x APLP2-KO, C57BL6 x 129S2; 5xFAD = Coexpression of 3 human APP mutations (Swedish, Florida, London) & 2 PS1 mutations (M146L; L286V), continuous backcross to B6SJLF1. Supp: UZH, ETH Zurich, NCCR Neuro, ZIHP.

Result summary and conclusions

We have collected data on 50 behavioral parameters of 863 mice. Subsequent factor analysis extracted 12 orthogonal factors accounting for 81% of total variance. Comparison of factor scores of C57BL/6, DBA/2, BALB/c and 129S2 mice revealed a unique profile for each strain. Analysis of mice with hippocampal, prefrontal, large dorsal cortical, habenular and striatal lesions also yielded unique profiles for each condition. Monitoring of mutant mice with known deficits in hippocampus-dependent tests produced profiles very similar to those of hippocampal lesions.

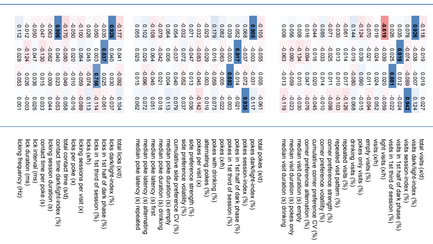
Thus, already the monitoring of spontaneous behavior during a few days of free adaptation to IntelliCage permits high throughput pre-screening of mutant mice. Comparison of the profile a new mutant line with those of known mutants or standard brain lesions provides a good starting point for the phenotyping and may already give hints which brains systems are affected. On the other hand, our data indicate that tight control of genetic background remains essential also if behavioral testing occurs in the home cage.

Factor analysis

- number and frequency
- spatial, diurnal and temporal distribution
- spatial sequence
- timing (latency, duration) and content

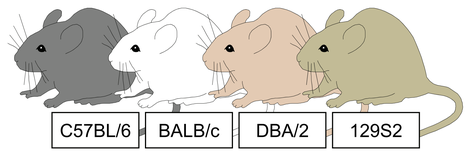
50 variables ⇨ 12 factors (81% variance) (orthogonal, varimax)

licks | pokes | visits



n=863

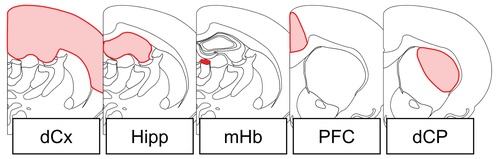
Strain profiles



C57BL/6	BALB/c	DBA/2	129S2		%	description
0.422	0.767	-0.400	-0.612	p<.0001	16%	many visits and pokes, preferentially lick-less
0.275	0.097	0.874	0.114	p<.0001	6%	large proportion of visits without pokes
-0.075	0.369	-0.103	1.614	p<.0001	9%	long visits with many pokes per visit
-0.192	-0.562	-0.210	-0.880	p<.0001	2%	long intervals between repeated pokes
-0.345	-0.122	-0.338	0.056	p<.0806	12%	little corner alternation, strong corner preferences
-0.526	0.285	0.396	-0.127	p<.0011	3%	little side alternation, strong side preferences
-0.427	-0.615	-0.761	0.262	p<.0001	11%	longer lick contact time, more licks per poke and overall
-0.430	0.761	0.547	0.485	p<.0001	4%	higher licking frequency and longer licks
-0.198	0.524	1.427	0.715	p<.0001	7%	activity more strongly focused on dark phase
-0.092	1.099	0.119	-0.393	p<.0001	5%	more of dark phase activity during first half
0.430	0.121	-0.181	-0.052	p<.3027	4%	more active during prospective drinking sessions
-0.075	-0.738	0.381	-1.183	p<.0001	3%	more of prospective session activity during first third
n=25	n=12	n=26	n=11			

strain means of factor scores

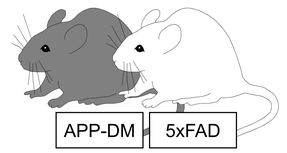
Lesion profiles



dCx	Hipp	mHb	PFC	dCP
0.288	0.787	0.548	-0.205	-0.289
1.956	-0.846	-0.792	0.036	-0.132
-2.386	-0.512	-0.049	0.024	0.031
1.565	0.438	0.425	0.517	1.092
3.126	1.763	0.035	-0.197	-0.269
1.865	-0.455	0.153	0.127	0.133
0.693	-0.386	-0.124	-0.122	0.208
1.010	0.292	-0.144	0.014	0.404
-0.448	0.529	-0.013	-0.157	0.323
-0.393	-0.199	0.695	-0.580	0.441
0.520	-0.082	0.283	-0.016	-0.571
-0.731	0.530	-0.188	0.891	-0.362
n=33	n=65	n=36	n=36	n=32

group differences of factor scores

Mutants



APP-DM	5xFAD
-0.029	-0.400
-1.185	-1.123
-1.269	0.507
-1.769	2.259
2.420	0.403
3.005	0.033
0.589	-0.203
0.090	-0.252
1.726	0.985
-0.112	0.219
0.374	0.097
0.593	0.255
n=21	n=31