PHENOSYS
Technology for Behaviour Analysis

TOUCHSCREEN CHAMBER
Touchscreen Paradigms

BACKGROUND

Over the last decade touchscreen methods for rodents have become an efficient and powerful diagnostic method. Touchscreens are now widely used for cognitive testing and therapeutic screening of rodent models for translational research. It permits behavioural, lesion, and pharmacological studies [1,2].

HARDWARE

The Touchscreen Chamber consists of a screen with an infrared-frame and a Skinner Box with a reward system.

SOFTWARE

The basic software allows the experimenter to control up to 16 Touchscreen Chambers per single computer. Test paradigms are available as the following single modules:

1. Autoshaping (AUTO)
2. 5-Choice Serial Reaction Time Task (5-CSRTT)
3. Extinction (EXT)
4. Paired associate learning (PAL)
5. Pattern Discrimination (PD; formerly Location Discrimination)
6. Trial-Unique-Nonmatching-to-Location (TUNL)
7. Two-Choice Visual Discrimination Learning and Reversal (2VDLR)
8. Three-Choice Visual Discrimination Learning and Reversal (3VDLR)
9. Two-Choice “Morph” Visual Discrimination (MVD)
10. Visuomotor Conditional Learning (VMCL)
11. Multidimensional Shifts (MULTI)
12. Transverse Patterning Task (TPT)

AUTOMATION

Fully automation is enabled by the ID-Sorter (not included), which allows the selective passage of a single animal to the Touchscreen Chamber and back to the home cage. It is controlled by RFID-technology (transponder).

[1] Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.
[2] Keeler, J. F. & Robbins, T. W. (2011). Translating cognition from animals to humans. Biochemical Pharmacology 81, 1356–1366.

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PARADIGMS

1. Autoshaping (AUTO) = Training Test

Duration 10 s | Food reward | Duration 10 s | No food reward

In Autoshaping rewards are given independent of the action of the animal. But this leads the animal to associate the conditioned stimulus (CS) with reward through classical conditioning. Subsequently, the animal transfers this knowledge to operant behaviour and begins to approach and touch the CS symbol on the screen (pavlovian instrumental transfer). Thus, in Autoshaping the stimulus predictive of reward (the CS+) comes to elicit responses, directed at that stimulus, that are normally elicited by the reinforcer alone. Visual stimuli are presented left or right on the touchscreen. The conditioned stimulus (the CS+) is always followed by reward; the other, the CS-, is never followed by reward. With training, rats come to approach the CS+ more often than the CS-. If Autoshaping is followed by a schedule where rewards are triggered by a correct touch action this combination of procedures leads the animal to automatically train itself to perform operant touch behaviour.

Clinical areas:

- Huntington's disease
- Schizophrenia

Manipulation	Region	Effect
Lesions of	the anterior cingulate cortex	Normal discriminated approach is not shown, significantly more approaches to the CS- are made
	the medial frontal cortex	Task normally acquired, but longer overall approach latencies
	the posterior cingulate cortex	No effect on acquisition
	the ventral striatum	Impair learning
Dopamine receptor antagonism and dopamine depletion within	the ventral striatum	Impair learning

Bussey, T. J., Everitt, B. J. & Robbins, T. W. (1997). Dissociable effects of cingulate and medial frontal cortex lesions on stimulus-reward learning using a novel Pavlovian autoshaping procedure for the rat: Implications for the neurobiology of emotion. Behavioral Neuroscience, 111 (5), 908–919.

Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.

2. 5-Choice Serial Reaction Time Task (5-CSRTT)

1. False 2. Correct

The 5-CSRTT requires the rodent to respond to a brief visual target stimulus that is presented in 5 possible locations. At its core, the task diagnoses attentional capacity through the accuracy of reporting the stimulus at the correct location. In addition, the task diagnoses inhibitory response control or executive functioning. Accuracy is measured as the percentage of correct responses from all responses. Incorrect responses, or errors of commission, refer to responses made where the target stimulus had not been presented.

At least two types of inhibitory response control can be indexed on the 5-CSRTT: firstly *premature responses*, which occur during the interval before the target stimulus has even been presented. Premature responses are generally interpreted as a form of impulsive behaviour. Secondly, *perseverative responses*, occur when rats continue to respond after the presentation of the target, akin to a form of compulsive over-responding. Several other behavioural variables are measured on the 5-CSRTT, including errors of omissions, latency to respond correctly, and reward collection latency.

Clinical areas:

- Alzheimer's disease
- Depression
- Huntington's disease
- Schizophrenia
- Attention deficit hyperactivity disorder (ADHD)
- Obsessive–compulsive disorder (OCD)

Manipulation	Region	Effects
Lesions of	the medial prefrontal cortex	Disturbances in response latency and choice
	the post-genual ACg cortex	Increase in impulsive responding, but no impairment in attentional performance
	the dorsomedial striatum	Decrements in response accuracy and increases in response latencies
Lesions encompassing	the ACg and PrL cortices	Impairment in choice accuracy and a slower latency to respond correctly
Neonatal lesions of	the ventral hippocampus	Mild impairments in choice accuracy and more pronounced increases in correct response latencies

Manipulation	Region	Effects
Infusions of 6-hydroxydopamine into	the dorsal noradrenergic ascending bundle	Impairment of the attentional accuracy
Infusions of dopamine D1 receptor agonists into	the medial prefrontal cortex	Enhancement of accuracy in animals having low baseline performance and impairment of accuracy in animals with high baseline performance
Infusions of the neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) into	the dorsal raphe´ nucleus	Increase in premature or impulsive responding and a transient improvement in accuracy
Bilateral injection of competitive NMDA antagonist (CPP) into	the medial prefrontal cortex	Reductions in choice accuracy, as well as increases in omissions and correct response latency
Repeated treatment with amphetamine		Impairments in choice accuracy and increased trial omissions under reduced stimulus duration conditions
Acute systemic administration of NMDA receptor antagonists MK-801 or PCP		Reductions in choice accuracy and response latencies
Repeated dosing of PCP		Reductions in discrimination accuracy, as well as increases in correct response latency and premature responses
Systemic administration of sulpiride	in medial prefrontal cortex-lesioned animals	Improvement of the impairment in attentional accuracy
Site-specific infusions of sulpiride into the nucleus accumbens		Improvement of the impairment in attentional accuracy
Acute administration of low doses of clozapine after acute MK-801 administration		Remediation of the accuracy deficits and increased omissions induced
Low doses of sertindole and clozapine		Prevent medial prefrontal cortex infusion of CPP-induced accuracy deficits
Oral aripiprazole and olanzapine (but not haloperidol)		Abolish a CPP-induced accuracy deficit

Manipulation	Region	Effects
Chronic treatment with clozapine		Attenuation of the reductions in accuracy, increase in premature responding following repeated PCP exposure
Imprinting centre deletion mouse model for Prader-Willi syndrome (PWS)		Decreased choice accuracy, increased omissions, and longer correct reaction times.

Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.

Dalley, J.W., Cardinal, R.N. & Robbins, T.W. (2004). Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neuroscience and Biobehavioral Reviews 28, 771–784.

3. Extinction (EXT)

1. Correct 2. False

Rodents are first required to respond to a visual stimulus to obtain a pellet: one white square in the center of the touchscreen is presented with a touch resulting in reward. Stimuli remain on the screen until a response is made. Once the acquisition criterion is reached, the response is then extinguished (i.e., no reward for touches).

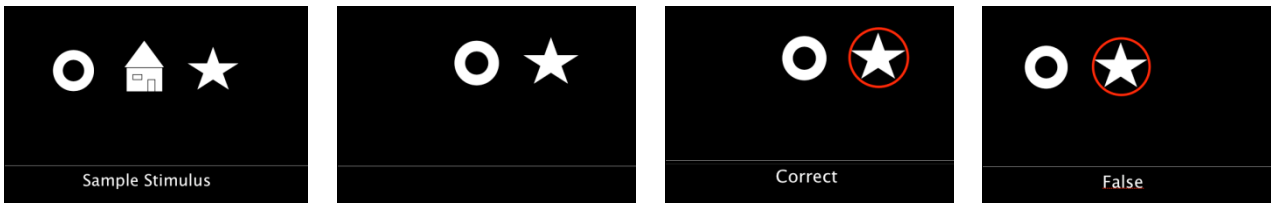
Clinical areas:

- Attention deficit hyperactivity disorder (ADHD)
- Obsessive–compulsive disorder (OCD)
- Schizophrenia

Brigman, J. L., Feyder, M., Saksida, L. M. et al. (2008). Impaired discrimination learning in mice lacking the NMDA receptor NR2A subunit. Learning Memory, 15, 50–54.

Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.

4. Paired associate learning (PAL)



Sample Stimulus Correct False

In the PAL task rodents have to learn and remember the correct spatial locations of three different objects. On a trial, two objects are presented on the touchscreen, one of them in the correct location, the other one in an incorrect location. The rodent has to touch the object that is in the correct location.
Alzheimer's disease patients in humans performing on a similar task and during the earliest stages of Alzheimer's disease can effectively be distinguished from patients that only suffer cognitive impairment caused by different etiologies.

Clinical areas:

- Alzheimer's disease
- Schizophrenia

Manipulation	Effect
Administration of glutamatergic antagonists	Impair performance
Deletions of the schizophrenia-associated gene *dlg2*	Severe impairment of PAL

Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.

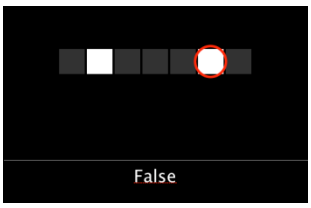
Talpos, J. C., Winters, B. D., Dias, R., Saksida, L. M. & Bussey, T. J. (2009). A novel touchscreen-automated paired-associate learning (PAL) task sensitive to pharmacological manipulation of the hippocampus: a translational rodent model of cognitive impairments in neurodegenerative disease. Psychopharmacology, 205, 157–168.

5. Pattern Discrimination (PD; formerly Location Discrimination)

1.

Correct

2.



False

The rodents are required to discriminate between two white squares on the screen. Responses to squares on one side of the screen will be rewarded, while responses on the other side of the screen will be punished with a time out period. The distance between the two squares is varied from trial to trial.

Clinical areas:

- Alzheimer's disease
- Schizophrenia
- Depression

Manipulation	Region	Effect
Lesions of	the dorsal hippocampus	Animals are impaired when the two choice locations are close together, but not when the locations are far apart
Increased neurogenesis by wheel-running		*Enhanced* pattern discrimination.

Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.

McTighe, S. M., Mara, A. C., Romberg, C., Bussey, T. J. & Saksida, L. M. (2009). A new touchscreen test of pattern separation: effect of hippocampal lesions. NeuroReport, 20, 881–885.

6. Trial-Unique-Nonmatching-to-Location (TUNL)

Correct

Like delayed nonmatching-to-place (DNMTP), the trial-unique nonmatching-to-location task (TUNL) uses only two locations in any given trial, but uses multiple locations across trials. In both tasks a sample location is presented to the subject and, following a delay, an additional location is presented that has to be touched by the rodent. By using multiple locations across trials pairs of locations are repeated much less often, and the task is closer to being trial-unique. In addition, the use of multiple locations decreases the potential to use mediating strategies. TUNL can be used to study spatial working memory or spatial pattern separation.
Hippocampal lesions: of hippocampal lesions.

Clinical areas:

- Alzheimer's disease
- Schizophrenia
- Depression

Manipulation	Region	Effect
Lesions of	the hippocampus	Highly sensitive to delay-dependent effects

Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.

Talpos, J. C., McTighe, S. M., Dias, R., Saksida, L. M. & Bussey, T. J. (2010). Trial-unique, delayed nonmatching-to-location (TUNL): A novel, highly hippocampus-dependent automated touchscreen test of location memory and pattern separation. Neurobiology of Learning and Memory, 94, 341–352.

7. Two-Choice Visual Discrimination Learning and Reversal (2VDLR)

Correct Correct False

In the Two-Choice Visual Discrimination Learning and Reversal task one of two visual stimuli is correct and will be rewarded with food. The stimuli are presented simultaneously and during subsequent trials at different locations. After reversal, the formerly unrewarded stimulus becomes the rewarded stimulus. Thus, the reinforcement contingencies are reversed such that a nose poke on the previous S+ is no longer rewarded. Reversal learning requires inhibition of prepotent responses and is known to be dependent on the prefrontal cortex.

Clinical areas:

- Huntington's disease
- Schizophrenia
- Parkinson's disease

Manipulation	Region	Effect
Lesions of	the prefrontal cortex	Impair performance
GLAST (EAAT-1, excitatory amino-acid transporter 1) knockout mice		Impaired acquisition
D1-like receptor antagonist		Impairment in early reversal trials

Bussey, T. J., Holmes, A., Lyon, L., Mar, A. C., McAllister, K. A., Nithianantharajah, J., Oomen, C. A. & Saksida, L. M. (2012). New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats. Neuropharmacology 62, 1191–1203.

Izquierdo, A., Wiedholz, L. M., Millstein, R. A., Yank, R. J., Bussey, T. J., Saksida, L. M. & Holmes, A. (2006). Genetic and dopaminergic modulation of reversal learning in a touchscreen-based operant procedure for mice. Behavioural Brain Research 171, 181–188.

8. Three-Choice Visual Discrimination Learning and Reversal (3VDLR)

Correct False False

Animals have to learn that one of three simultaneously presented visual stimuli is correct and will be rewarded with food. After reversal, one formerly unrewarded stimulus becomes the rewarded stimulus.

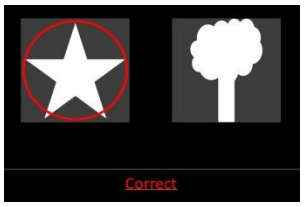
Clinical areas:

- Schizophrenia
- Obsessive–compulsive disorder (OCD)

Manipulation	Effect
Injections of SB242084, a 5HT2C antagonist (serotonergic modulation of cognitive flexibility)	Visual reversal learning impaired
Injections of M100907 (5HT2A antagonist) and WAY163909 (5HT2C agonist)	Responding transiently reduced
Injections of 5HT2C antagonist SB242084	Responding increased

Alsiö, J., Mar, A. C., Theobald, D. E., Robbins, T. W. (2011). Visual discrimination and reversal learning in a novel touch screen task is differentially modulated by 5-HT(2A) and 5-HT(2C) antagonists in rats. Poster presentation, 43rd Annual General Meeting of the European Brain and Behaviour Society (EBBS) in Seville.

9. Two-Choice “Morph” Visual Discrimination (MVD)



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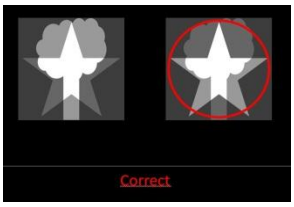
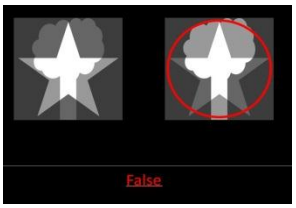


Correct (“star morph”)



False (“tree morph”)

In this task the animals are first trained with the stimuli of the regular two-choice visual discrimination task (7.). Subsequently, the test stimuli are “morphed” (blended) versions of the training stimuli: “star morph” containing 60% star and 40% tree, and “tree morph” containing 60% tree and 40% star. Acquisition of this task has been shown to be dependent on cholinergic and glutamatergic function within the perirhinal cortex.

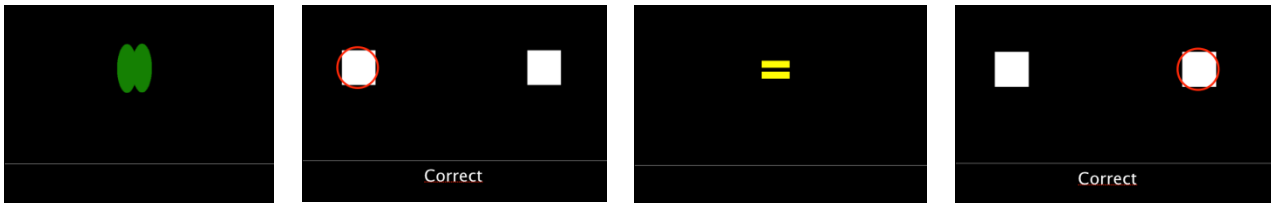
Clinical area:

- Alzheimer’s disease

Manipulation	Effect
Low doses of FK962 (promotes somatostatin production) and donepezil (an acetylcholinesterase inhibitor)	Cognition enhancement

McCarthy, A. D., Owens , I. J., Bansal, A. T., McTighe, S. M., Bussey, T. J. & Saksida, L. M. (2011). FK962 and donepezil act synergistically to improve cognition in rats: Potential as an add-on therapy for Alzheimer's disease. Pharmacology, Biochemistry and Behavior. 98, 76–80.

10. Visuomotor Conditional Learning (VMCL)



Correct Correct

In the visuomotor conditional learning task (VMCL) subjects are required to learn a rule of the type “If stimulus A then go left, if stimulus B then go right”.

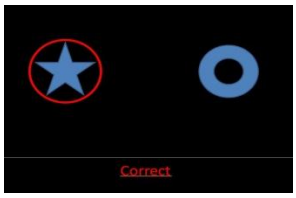
Clinical areas:

- Huntington’s disease
- Parkinson’s disease

Manipulation	Region	Effect
Lesions of	the dorsal striatum	Impair performance

Chudasama, Y., Bussey, T. J. & Muir, J. L. (2001). Effects of selective thalamic and prelimbic cortex lesions on two types of visual discrimination and reversal learning. European Journal of Neuroscience, 14, 1009–1020.

11. Multidimensional Shifts (MULTI)



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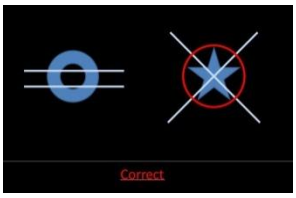

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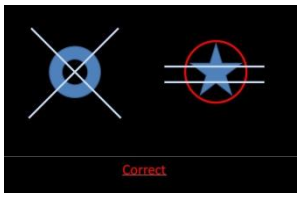

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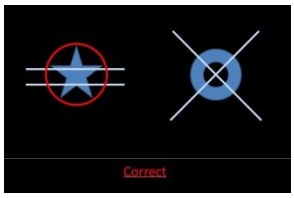

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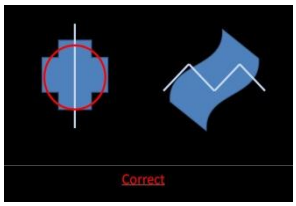

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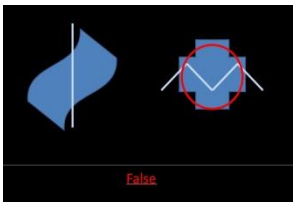
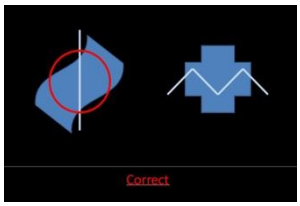


False



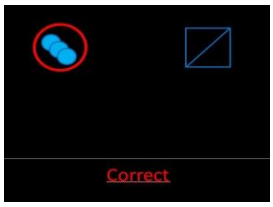
Correct

In this task subjects are trained to attend to 1 of 2 stimulus dimensions (lines or shapes). On a 2nd problem with new stimuli, the subjects are required to attend to the same dimension (intradimensional [ID] shift) or switch to the previously irrelevant dimension (extradimensional [ED] shift).

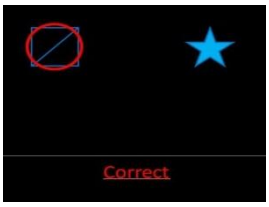
Manipulation	Region	Effect
Lesions of	the prefrontal cortex	Impair performance

Brigman, J. L., Bussey, T. J., Saksida, L. M. & Rothblat, L. A. (2005). Discrimination of Multidimensional Visual Stimuli by Mice: Intra- and Extradimensional Shifts. Behavioral Neuroscience. 119 (3), 839–842.

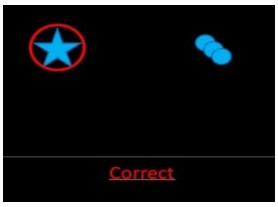
12. Transverse Patterning Task (TPT)



Correct (A+/B-)



Correct (B+/C-)



Correct (C+/A-)

The transverse patterning task involves the concurrent solution of three discrimination problems: stimulus A+ versus B-; stimulus B+ versus C-; and stimulus C+ versus A-.

Manipulation	Region	Effect
Lesions of	the fornix	Significantly *facilitated* performance (impaired performance on T-maze alternation and the Morris Swim Task)

Bussey, T. J., Warburton, E. C., Aggleton, J. P. & Muir, J. L. (1998). Fornix lesions can facilitate acquisition of the transverse patterning task: a challenge for “configural” theories of hippocampal function. The Journal of Neuroscience, 18 (4), 1622–1631.