Robust and translationally relevant measures of cognition in rodents

Improving procedures and data interpretation in behavioural neuroscience

- Interpreting the relevance of behavioral data for cognitive function
- Behavioral paradigms with better (i) resolution, (ii) sensitivity, for collecting reproducible data.
- Steps to promote the adoption of these paradigms over traditional assays
- Combining modern behavioral paradigms with brain manipulations

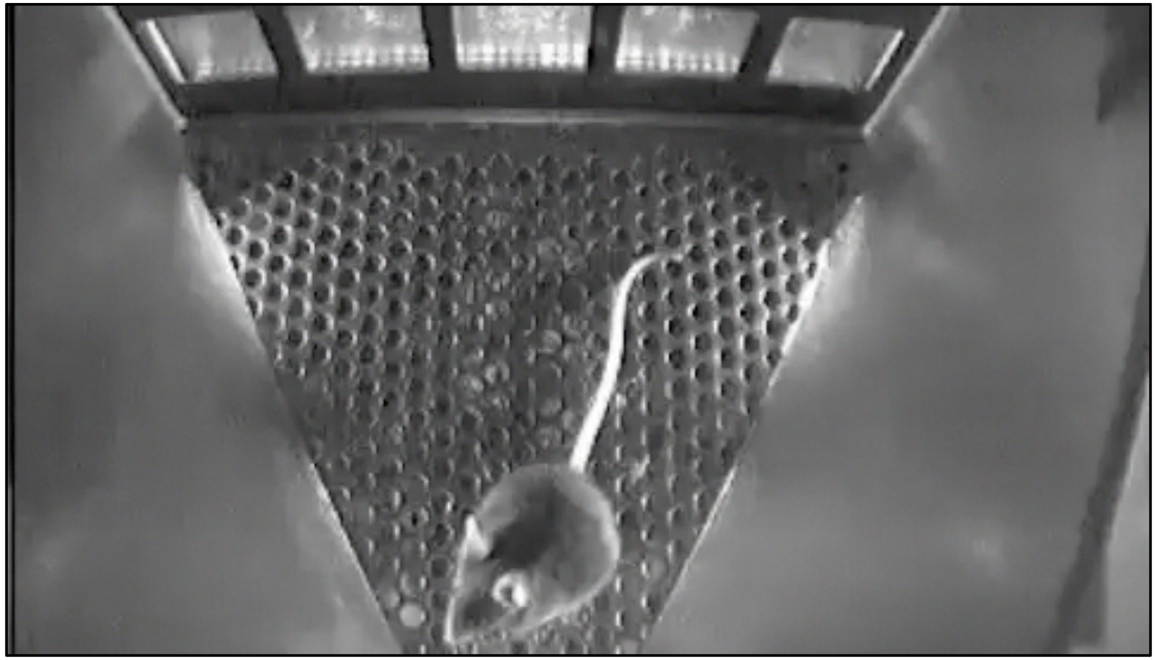
What is a **cognitive** phenotype? (attention / impulsivity)

ATTENTION / IMPULSIVITY IN THE 5-CHOICE SERIAL REACTION TIME TASK

- Attentional function primarily determined by % accuracy.
  Impulsivity primarily determined % premature responses.
  E.g. Increased number of omissions is per se not an attention deficit

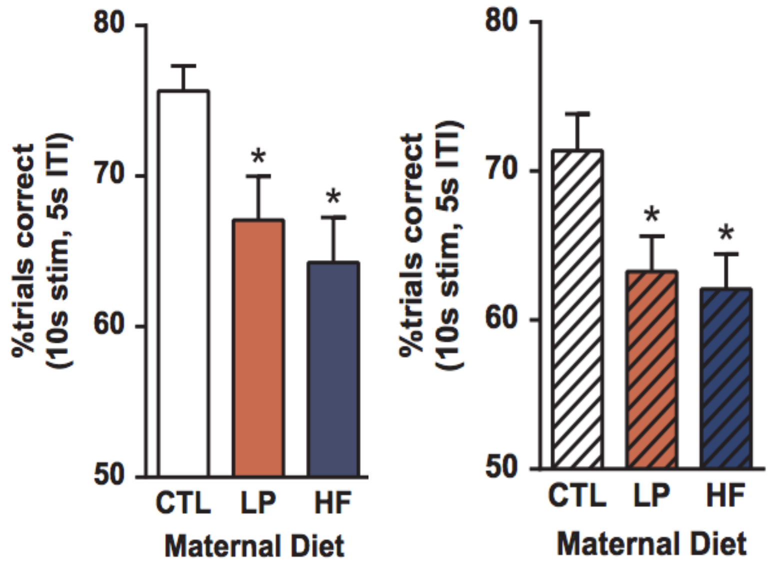
- Manipulation affects performance and not learning.
  E.g., attentional deficits do not disappear with repeated testing

- <u>Effect of manipulation directly related to task difficulty</u>
  E.g., attention effect present at short SDs / absent at long SDs; impulsive effect present at long delays / absent at short delays; Sustained attention deficit present at long sessions / absent at short delays sessions

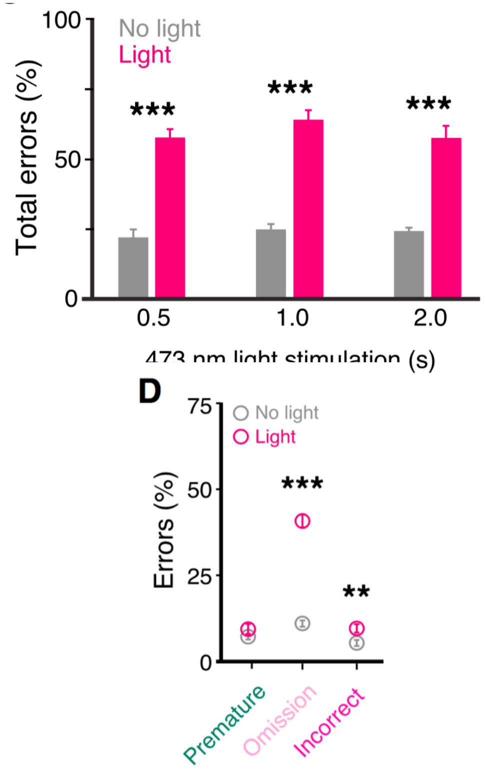


Reports of “attentional” phenotypes in rodents

Neuropsychopharmacology (2015) 40, 1353–1363

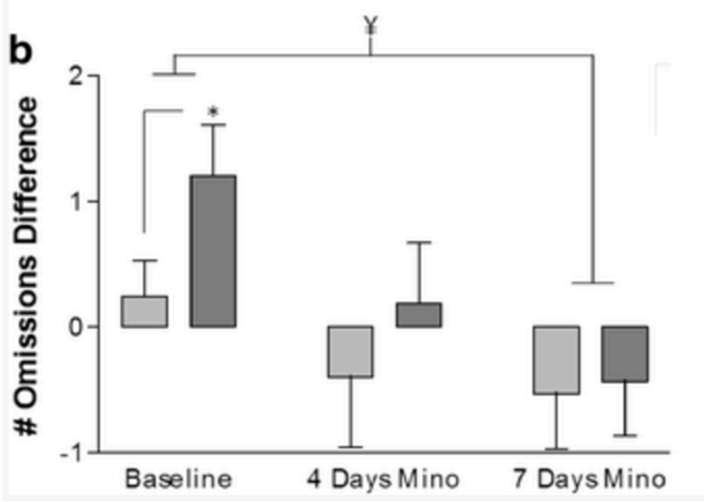


Cell 164, 208–218, January 14, 2016 ©2016



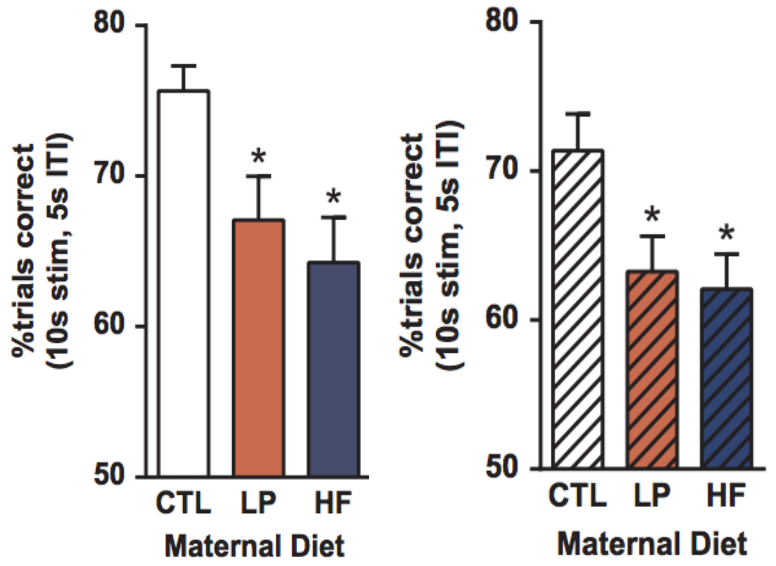
Psychopharmacology Accepted: 10 October 2016
DOI 10.1007/s00213-016-4463-y

ORIGINAL INVESTIGATION

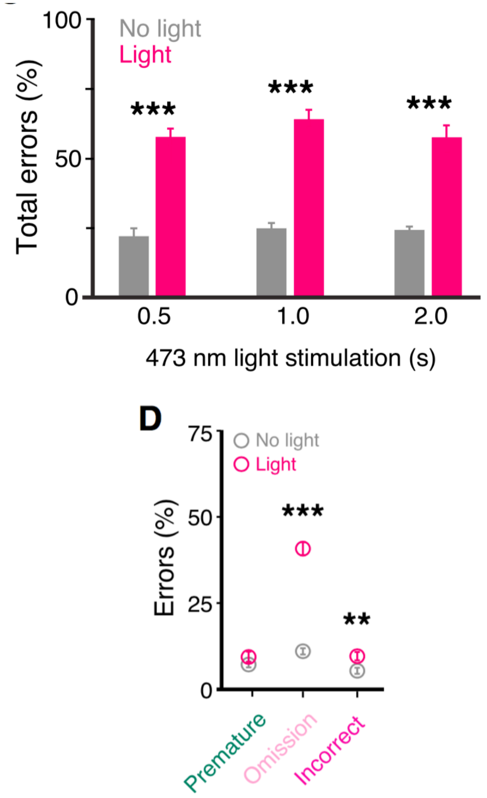


Reports of "attentional" phenotypes in rodents

Neuropsychopharmacology (2015) 40, 1353–1363

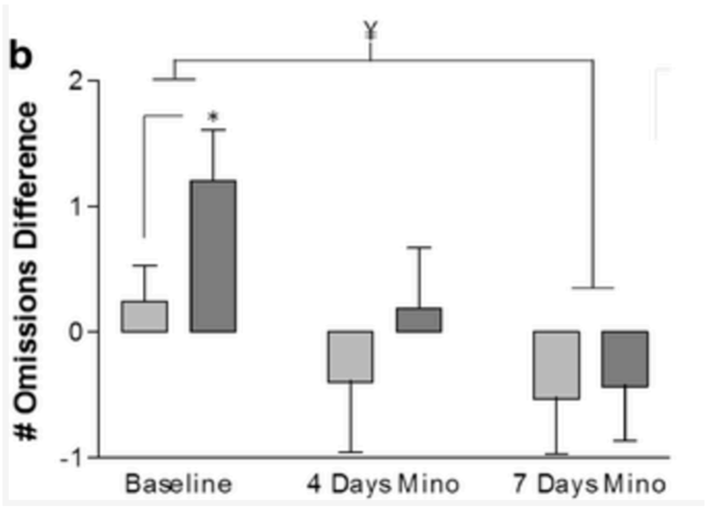


Cell *164*, 208–218, January 14, 2016 ©2016



Psychopharmacology Accepted: 10 October 2016
DOI 10.1007/s00213-016-4463-y

ORIGINAL INVESTIGATION



Are the 'attentional' phenotypes removed or exaggerated when manipulating the attentional component of task?

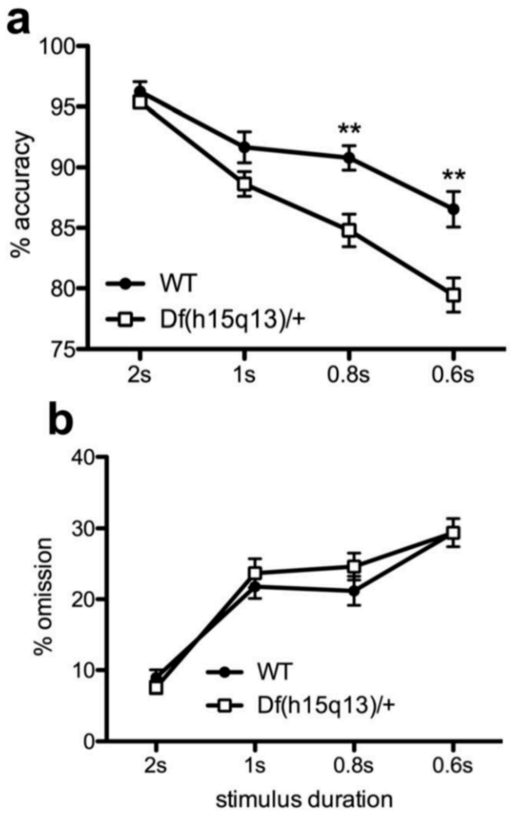
No

Could we get the similar results by tying ball-bearings to the animals legs?

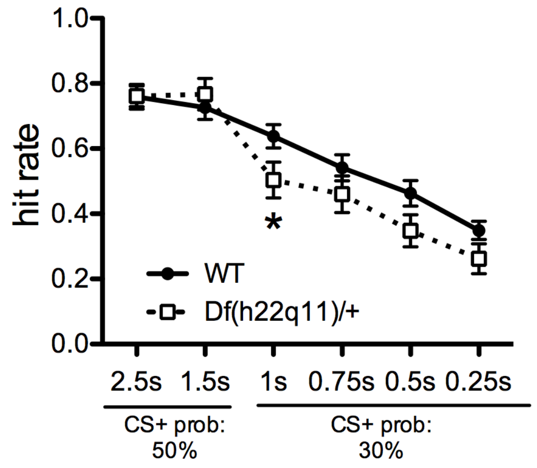
Possibly

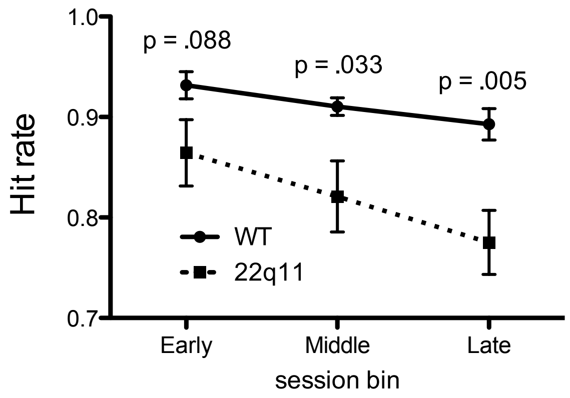
Attentional/Impulsive phenotypes in CNV models

Psychopharmacology (2016) 233:2151–2163
DOI 10.1007/s00213-016-4265-2

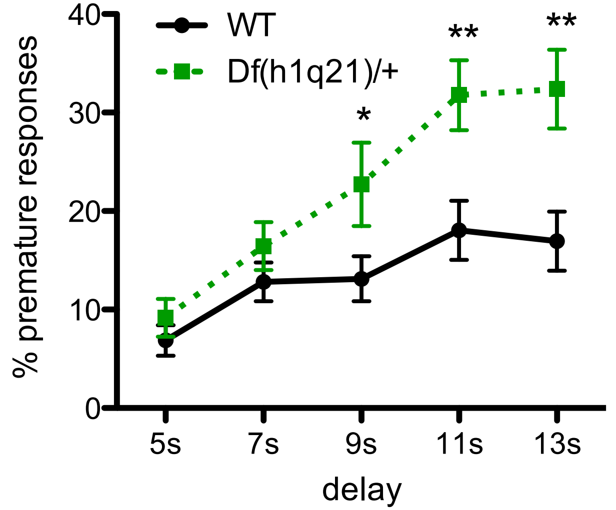


Attentional impairment in 15q13 CNV model





Attentional impairment in 22q11 CNV model



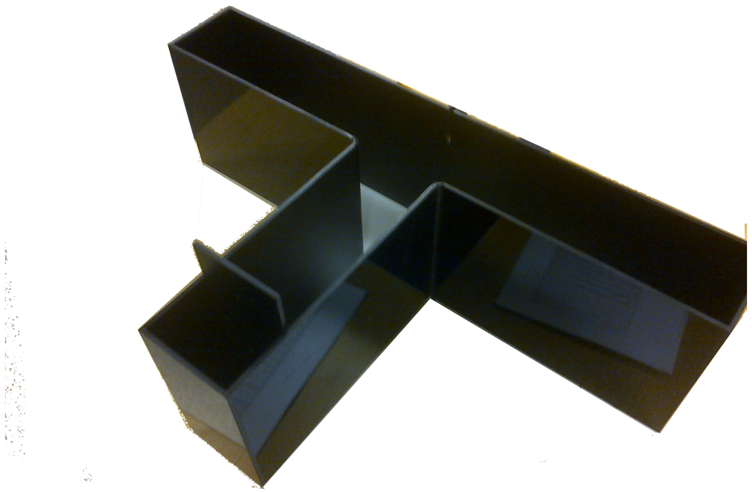
Impulsive deficit in 1q21 CNV model

EFFECTS OF MANIPULATIONS ARE ONLY OBSERVED AFTER CAREFUL MANIPULATIONS OF TASK PARAMETER MEASURING ON THE COGNITIVE CONSTRUCT OF INTEREST

What is a **cognitive** phenotype? (Working memory)

SPATIAL WORKING MEMORY IN T-MAZE

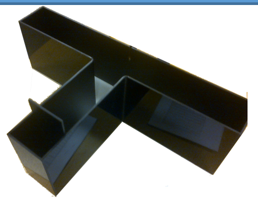
- The manipulation affects performance and not learning.
  E.g., phenotype do not disappear with repeated testing

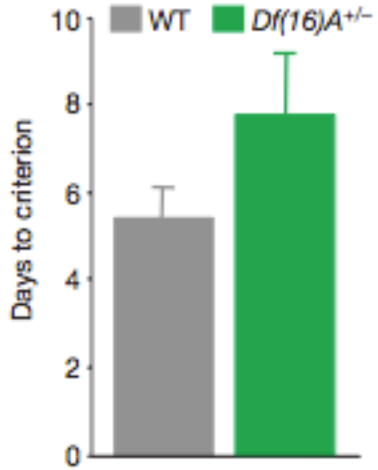


- Effect of manipulation directly related to task difficulty.
  E.g., phenotype is present at long delays but not short delays

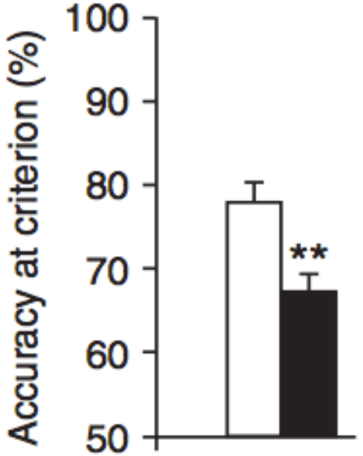
What is a **cognitive** phenotype? (Working memory)

SPATIAL WORKING MEMORY IN T-MAZE





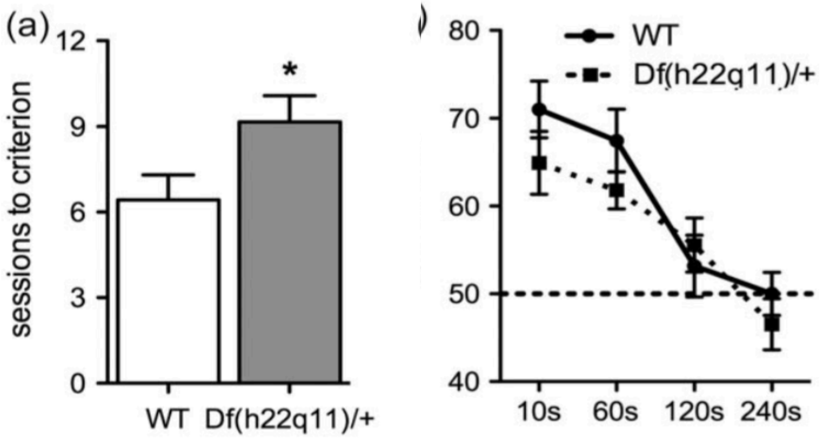
nature LETTERS



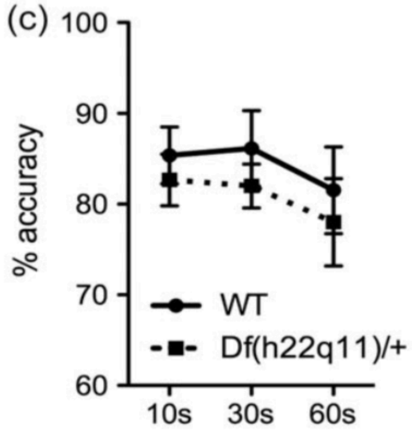
NATURE GENETICS
VOLUME 40 | NUMBER 6

"Working memory" deficits in 22q11 CNV mouse model expressed as a learning deficit. No manipulation of delay.

"Working memory" deficits in 22q11 CNV mouse model is delay-independent and a learning deficit.



Automated T-maze



Josh Gordon, Columbia protocol

Cerebral Cortex, October 2016;26: 3991–4003
Simon RO. Nilsson[1,2,3], Kim Fejgin[4], Francois Gastambide[5], Miriam A. Vogt[6], Brianne A. Kent[1,2], Vibeke Nielsen[4], Jacob Nielsen[4], Peter Gass[6], Trevor W. Robbins[1,2], Lisa M. Saksida[1,2], Tine B. Stensbøl[4], Mark D. Tricklebank[5], Michael Didriksen[4], and Timothy J. Bussey[1,2]

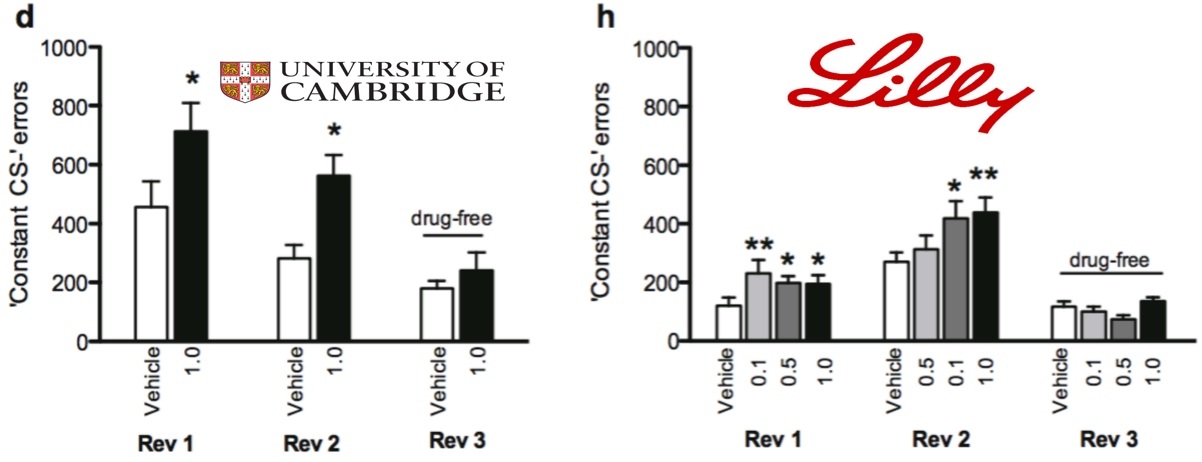
BEHAVIOURAL PHENOTYPES MIS-REPRESENTED AS TRANSLATIONALLY RELEVENT

REPRODUCABILITY

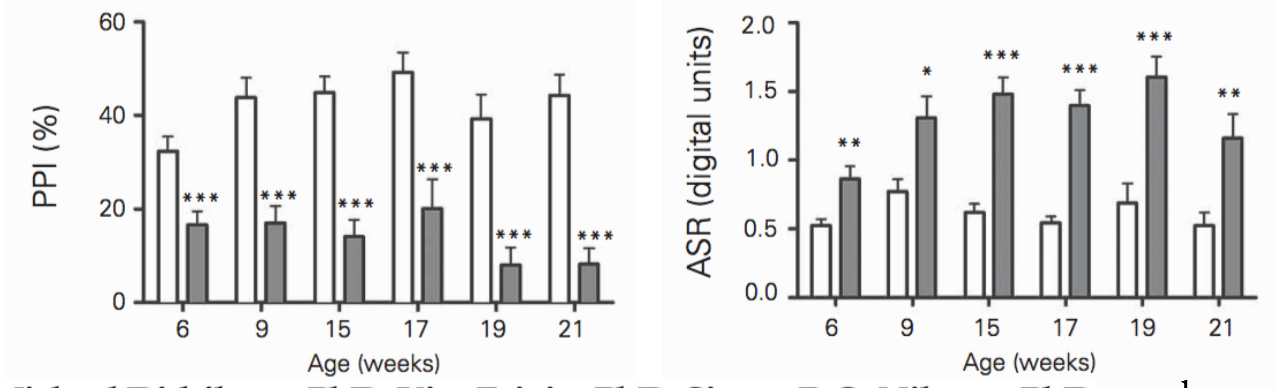
Psychopharmacology (2015) 232:4017–4031
DOI 10.1007/s00213-015-3963-5

ORIGINAL INVESTIGATION

J. Alsiö[1,2,3] · S. R. O. Nilsson[1,2] · F. Gastambide[4] · R. A. H. Wang[1,2] · S. A. Dam[1,2] · A. C. Mar[1,2] · M. Tricklebank[4] · T. W. Robbins[1,2]

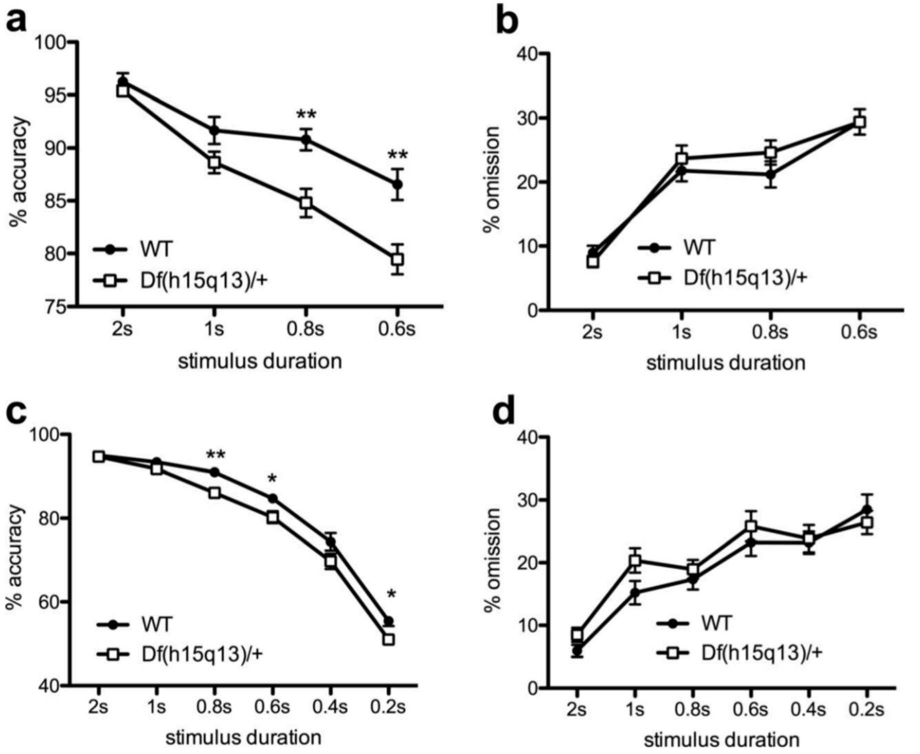


J Psychiatry Neurosci July 12, 2016



Michael Didriksen, PhD; Kim Fejgin, PhD; Simon R.O. Nilsson, PhD, et al.

Psychopharmacology (2016) 233:2151–2163
DOI 10.1007/s00213-016-4265-2



Simon R. O. Nilsson[1,2,3] · Pau Celada[4,5] · Kim Fejgin[6] · Jonas Thelin[6,7] · Jacob Nielsen[6] · Noemí Santana[4,5] · Christopher J. Heath[1,2,8] · Peter H. Larsen[6] · Vibeke Nielsen[6] · Brianne A. Kent[1,2] · Lisa M. Saksida[1,2] · Tine B. Stensbøl[6] · Trevor W. Robbins[1,2] · Jesper F. Bastlund[6] · Timothy J. Bussey[1,2] · Francesc Artigas[4,5] · Michael Didriksen[6]

REPRODUCE / REPLICATE RESULTS WITHIN OR ACROSS SITES

Improved task sensitivity (attention / impulsivity)

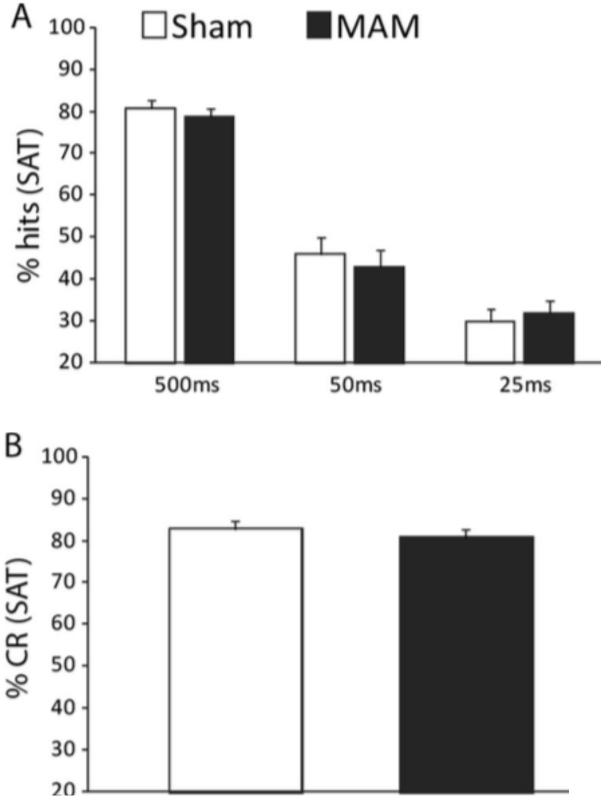
Neuropsychopharmacology (2007) 32, 483–492

Table 2 Effects of MAM on 5-Choice Performance with a Shortened Stimulus Duration

Measure	**Group**	**Stimulus duration (s)**			
		1	**0.5**	**0.25**	**0.125**
(A) Accuracy	SAL	91.2 (1.3)	74.3 (3.5)	62.9 (3.6)	46.0 (3.1)
	MAM	86.4 (2.0)	77.7 (3.3)	58.4 (2.5)	49.7 (3.6)
(B) Premature	SAL	8.6 (3.0)	6.3 (2.2)	10.3 (4.04)	6.0 (1.5)
	MAM	7.6 (1.4)	8.4 (1.5)	10.3 (2.92)	14.6 (3.4)
(C) Omission	SAL	9.7 (1.9)	25.3 (4.9)	36.7 (6.2)	43.8 (6.6)
	MAM	6.8 (1.9)	15.3 (6.2)	25.6 (6.2)	31.4 (5.4)
(D) Perseverative	SAL	7.3 (1.3)	3.8 (1.1)	1.8 (0.5)	1.0 (0.4)
	MAM	5.7 (0.8)	3.4 (0.5)	2.5 (0.6)	3.3 (0.5)
(E) Correct lat	SAL	0.98 (0.16)	0.78 (0.09)	0.69 (0.06)	0.66 (0.05)
	MAM	0.87 (0.08)	0.75 (0.11)	0.59 (0.04)	0.61 (0.03)
(F) Reinforce lat	SAL	0.9 (0.02)	0.93 (0.02)	0.94 (0.03)	0.98 (0.03)
	MAM	0.99 (0.16)	1.02 (0.03)	1.06 (0.05)	1.03 (0.04)

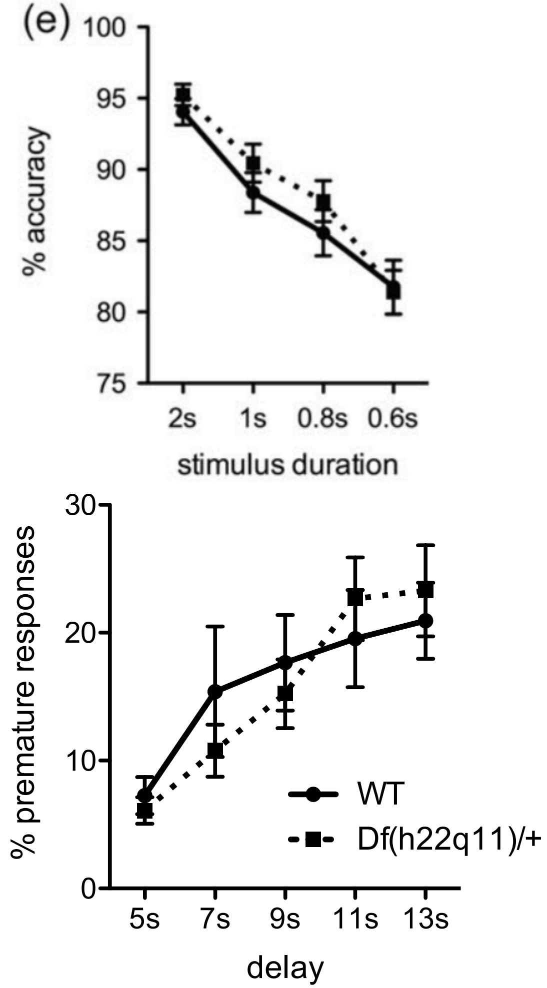
No 5CSRTT attention deficit in MAM-E17 model

Psychopharmacology (2015) 232:4113–4127



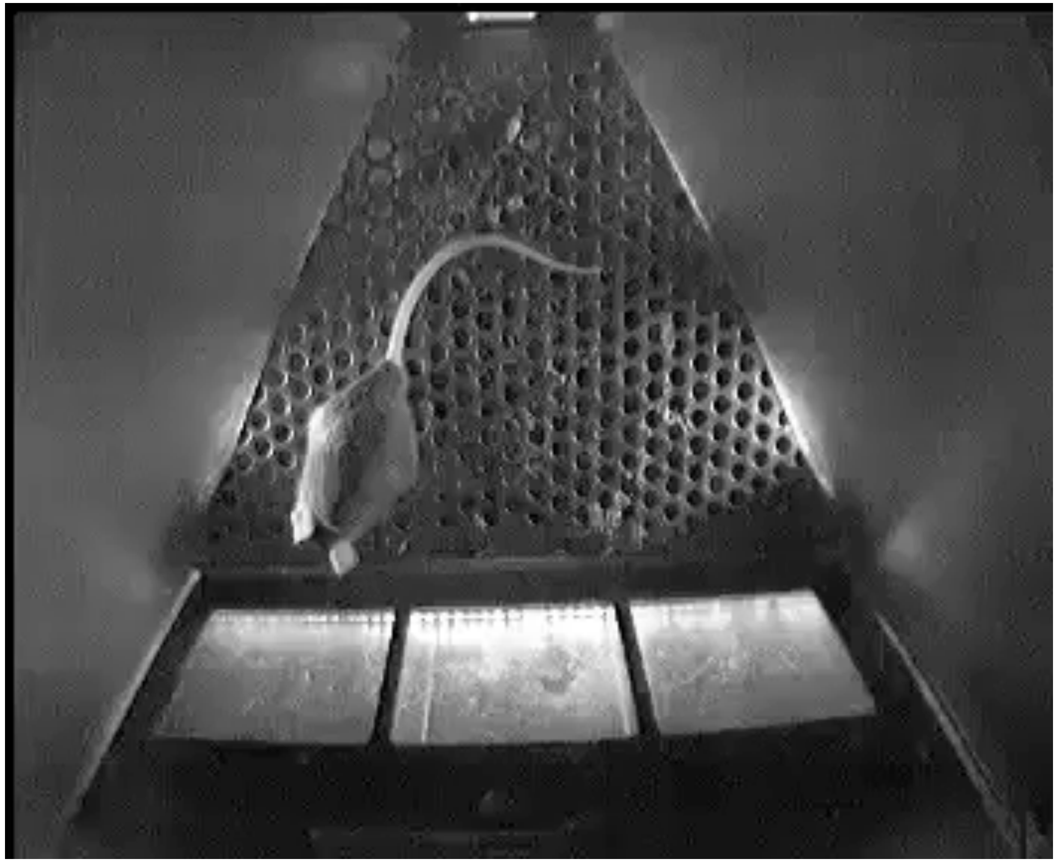
No dSAT attention deficit in MAM-E17 model – attention impairments typical in schizophrenia patients

Cerebral Cortex, October 2016;26: 3991–4003



No 5CSRTT attention deficit in 22q11 model – strongly linked to attention in patient

Improved task sensitivity (attention / impulsivity)



Mouse rCPT task

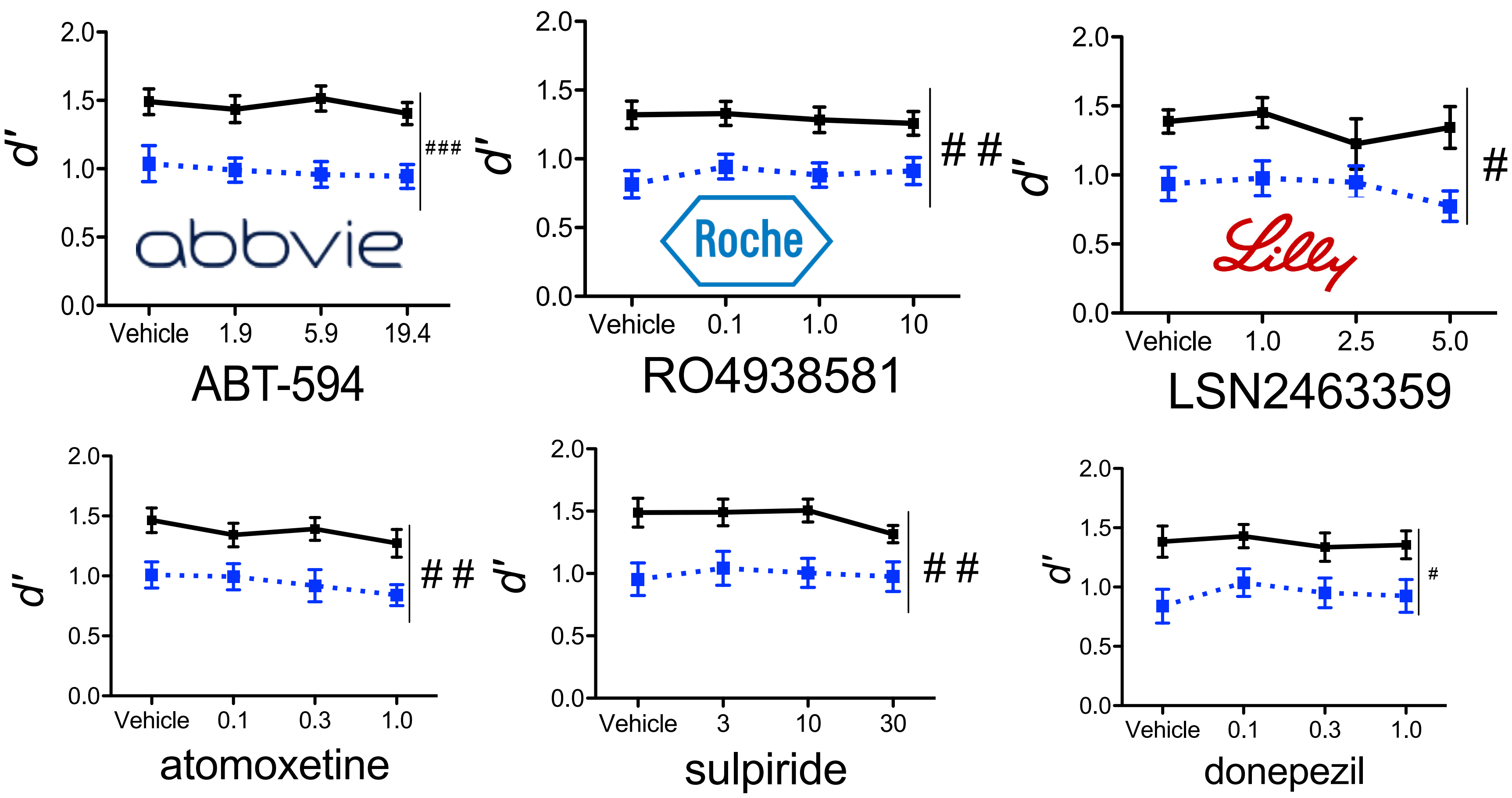
Psychopharmacology (2015) 232:3947–3966

Chi Hun Kim[1] • Martha Hvoslef-Eide[1] • Simon R. O. Nilsson[1] • Mark R. Johnson[2] • Bronwen R. Herbert[2] • Trevor W. Robbins[1] • Lisa M. Saksida[1] • Timothy J. Bussey[1] • Adam C. Mar[1,3]

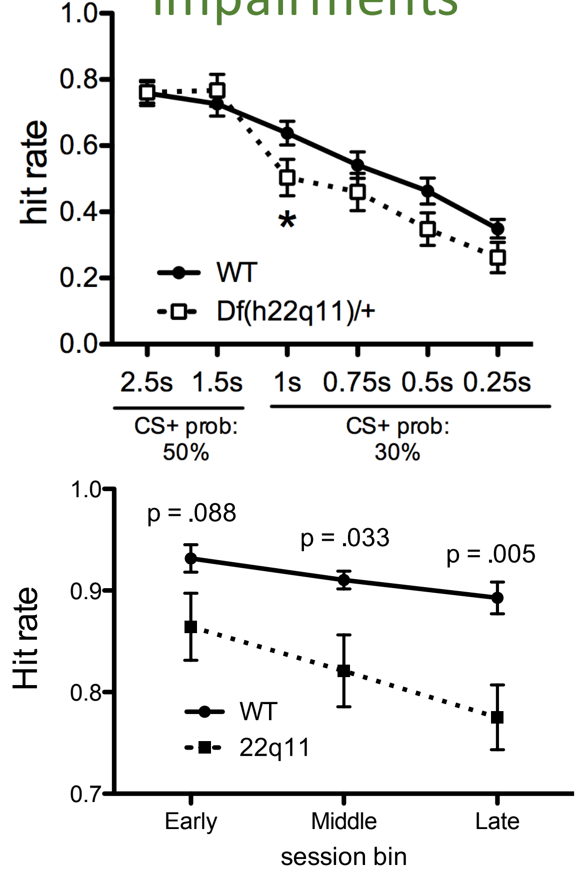
Rat rCPT task

RODENT CPT DETECT REPRODUCABLE IMPAIRMENTS WHERE OTHER TASKS DON’T

MAM-E17 associated impairment not attenuated by 8 compounds



22q11 CNV has replicable impairments



CPT has robust sensitivity for detecting impairments in animal models

TASKS WITH IMPROVED SENSITIVITY – reversal learning

REVERSAL LEARNING

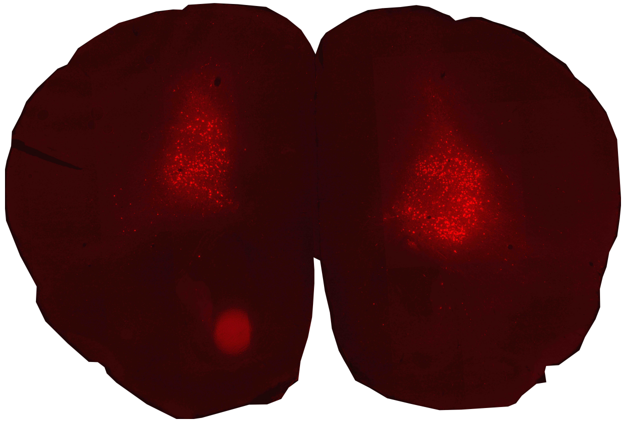
Task do not discriminate between patient populations or between disease models

NATURE PROTOCOLS | VOL.8 NO.10 | 2013 | 1985
Adam C Mar[1,2], Alexa E Horner[1–3], Simon R O Nilsson[1,2], et al.

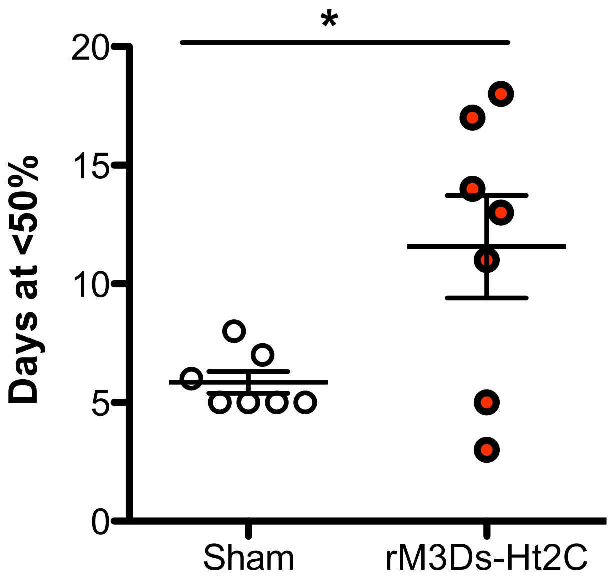
Table 1
Observations of cognitive inflexibility in psychiatric disorders in reversal learning and attentional set-shifting tasks.

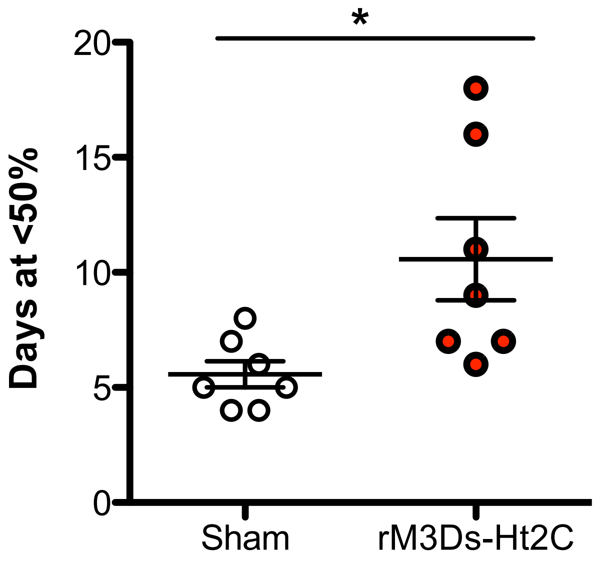
Underlying condition	Deficit observed in	Reference
Parkinson's disease	Spatial reversal learning	Freedman and Oscar-Berman (1989)
	CANTAB ED perseverance/learned irrelevance probes	Owen et al. (1993)
	CANTAB ED learned irrelevance probe	Slabosz et al. (2006)
	Probabilistic visual reversal learning	Cools et al. (2001)
	CANTAB set-shifting and reversal learning	Downes et al. (1989)
Alzheimer's disease	Spatial reversal learning	Freedman and Oscar-Berman (1989)
	Object reversal learning	Freedman and Oscar-Berman (1989)
OCD	Probabilistic visual reversal learning	Remijnse et al. (2006)
	CANTAB set-shifting	Chamberlain et al. (2006)
	CANTAB set-shifting and Go/No-go reversal learning	Watkins et al. (2005)
Schizophrenia	CANTAB ED perseverance probe	Elliott et al. (1995, 1995)
	CANTAB set-shifting and reversal learning	Ceaser et al. (2008), Jazbec et al. (2007), Leeson et al. (2009), Murray et al. (2008), Pantelis et al. (1999)
Autism	Spatial reversal learning	Coldren and Halloran (2003)
	Probabilistic reversal learning	D'Cruz et al. (2013)
	CANTAB set-shifting and reversal learning	Hughes et al. (1994), Ozonoff et al. (2004)
	CANTAB set-shifting	Ozonoff et al. (2000)
Unipolar depression	Probabilistic visual reversal learning	Reischies (1999)
	WCST	Martínez-Arán et al. (2004), Merriam et al. (1999)
	CANTAB set-shifting and reversal learning	Taylor Tavares et al. (2007)
Bipolar depression	CANTAB set-shifting and reversal learning	Clark et al. (2001), McKirdy et al. (2009)
	Probabilistic visual reversal learning	Gorrindo et al. (2005)
	Go/No-go reversal learning	Holmes et al. (2008), Murphy et al. (1999)
	Attentional set-shifting	Clark et al. (2005)
	CANTAB set-shifting	Clark et al. (2002)
	CANTAB reversal learning	Dickstein et al. (2004)
	WCST	Martínez-Arán et al. (2004)
Huntington's disease	CANTAB set-shifting and reversal learning	Lange et al. (1995), Lawrence et al. (1996)
	CANTAB ED perseverance probe	Lawrence et al. (1999)
	Object reversal learning	Oscar-Berman and Zola-Morgan (1980)
	CANTAB set-shifting	Lawrence et al. (1998)
ADHD	Go/No-go reversal learning	Itami and Uno (2002)
	WCST	Reeve and Schandler (2001)
	CANTAB set-shifting and reversal	Gau and Shang (2010), Kempton et al. (1999)
Cocaine abuse	Probabilistic reversal learning	Ersche et al. (2008)

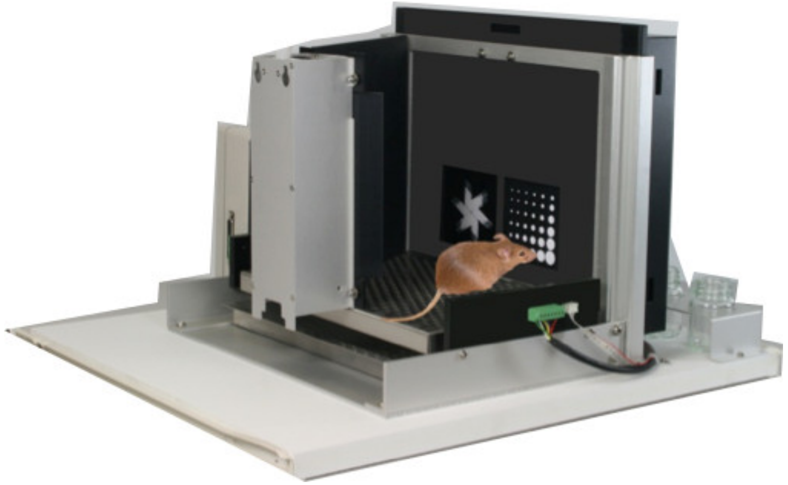
Simon R.O. Nilsson[a,b,*], Johan Alsiö[a,b,e], Elizabeth M. Somerville[c], Peter G. Clifton[d]
Neuroscience and Biobehavioral Reviews 56 (2015) 1–14



mCherry expression after rM3Ds infusion in 5-HT2C cre mice

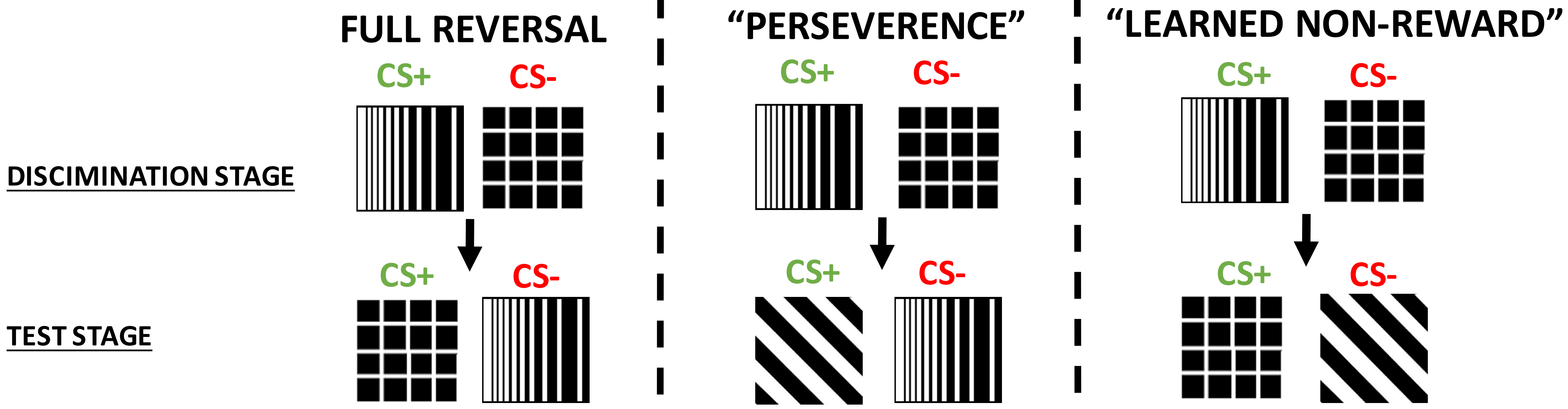






EXPERIMENT 5: Systemic clozapine-N-oxide (3 mg/kg, i.p.) impaired early reversal learning without affecting late reversal learning in intra-OFC rM3Ds treated 5-HT2C Cre-positive mice.

NEW TASKS WITH IMPROVED SENSITIVITY – reversal learning



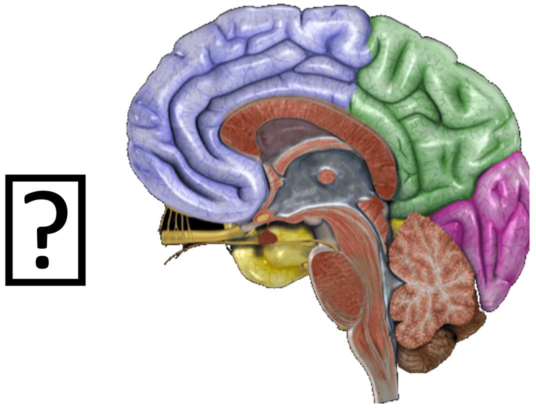
Test ability to overcome positive and negative associations

Test ability to overcome positive association

Test ability to overcome negative association

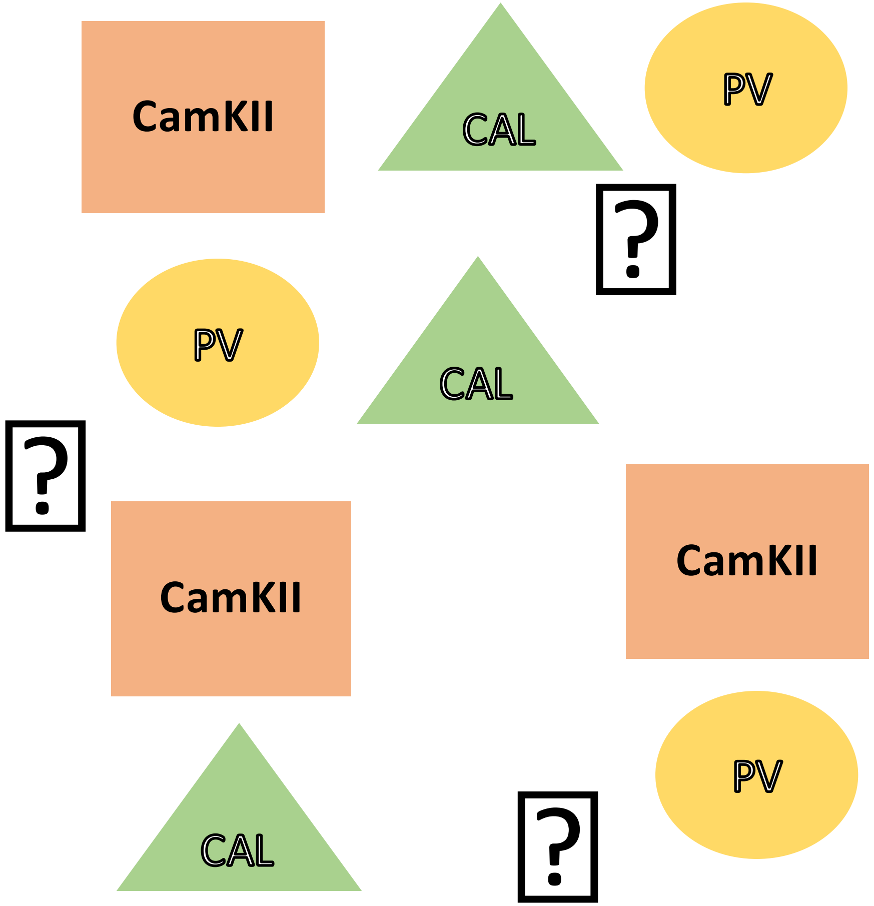
TARGET CURCUITS THROUGH ACTIVITY-DEPENDENT MARKERS

Anatomical target
(e.g., local drug infusions/lesions)



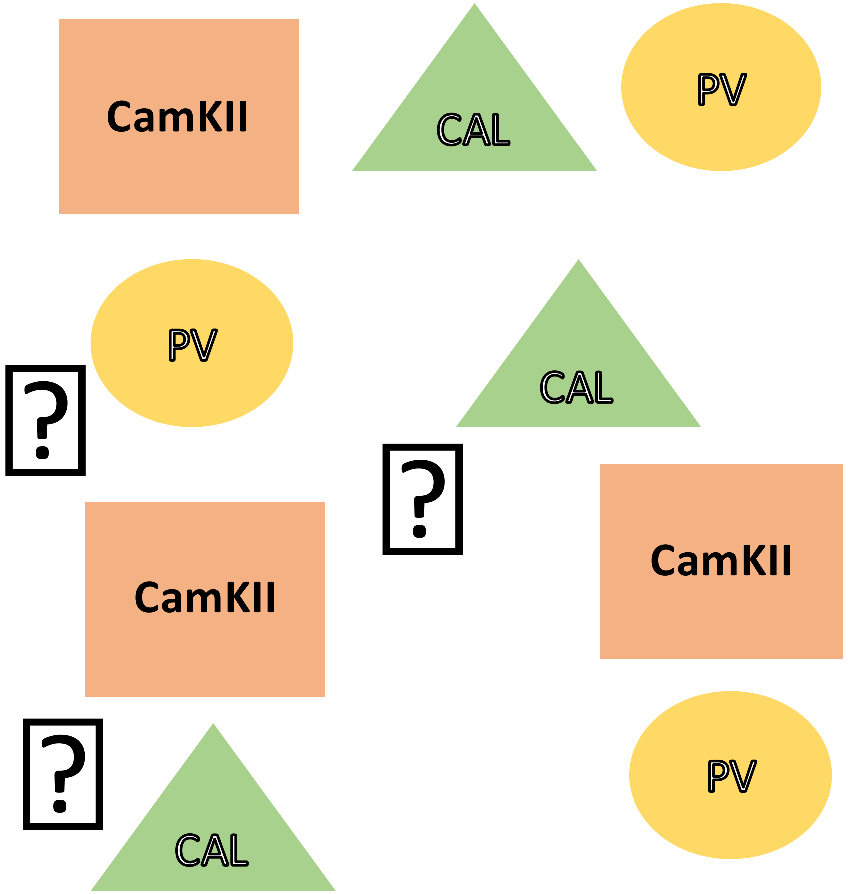
Targets entire brain area irrespective of role in cognition

Molecular targeting
(e.g. PV+ dependent opsins/DREADDs)



Targets local cells irrespective of role in cognition

Activity-dependent targeting
(e.g., cFos driven opsin/DREADDs/LacZ)



Allows access to cognition-specific cells irrespective of molecular phenotype

PROMOTE USE OF MODERN BEHAVIOURAL PARADIGMS

- Make reliable hardware readily available
- Produce standardised open-source code
- Expert troubleshooting advice
- Improve hardware for decreasing man-hours and more more data collection

TRUE high-throughput pharmacology
(i.e., allow near-daily screens of new compounds)

Robust models

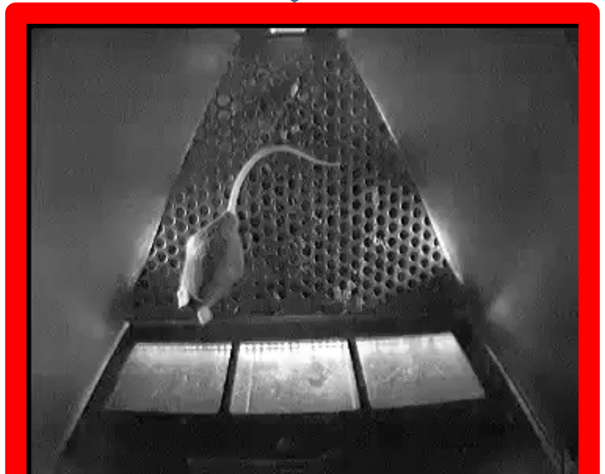
W/ (i) construct validity,
(ii) **stable**, relevant cognitive deficits

Mate w/ transgenic lines

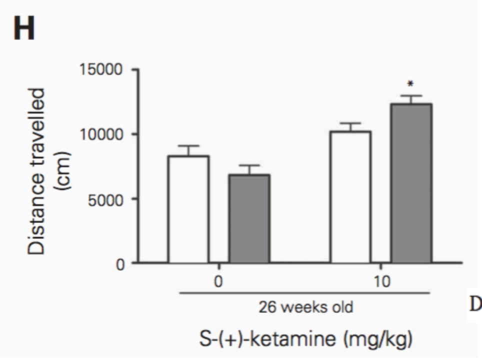
(induce molecular-/activity-dependent markers)
To allow causative inferences through transient manipulations

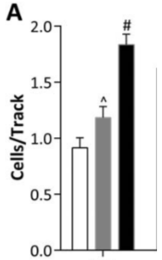
In-vivo behavioural correlates

(e.g., ephys / imaging / amperometry)
To allow mechanistic insight



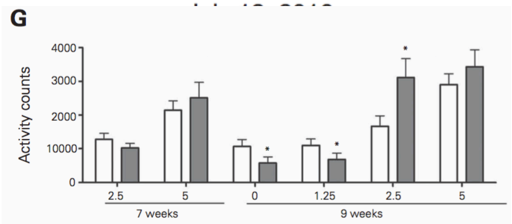
CLEAR MOLECULAR / CUITCUITRY PHENOTYPES IN ANIMAL MODELS



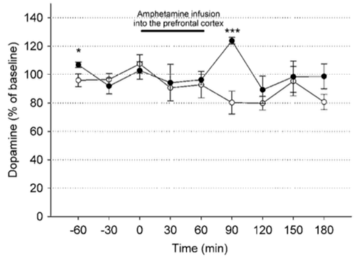


Developmental Neurobiology accepted 13 February 2014

J Psychiatry Neurosci

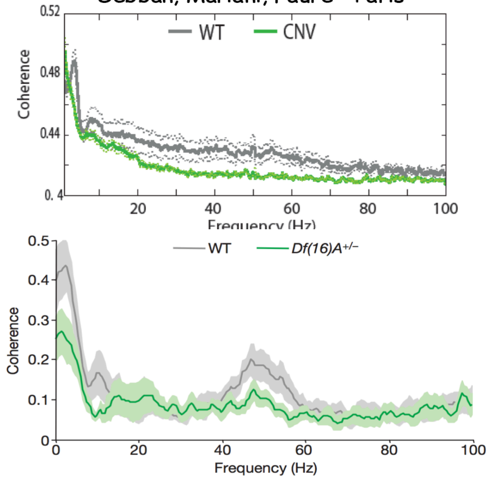


Neuropsychopharmacology (2004) 29, 2052–2064



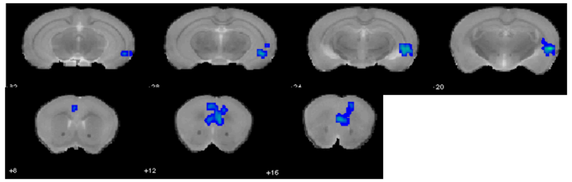
DA-hyperfunctions

Sebban, Mariani, Faure - Paris



NATURE | Vol 464 | 1 April 2010

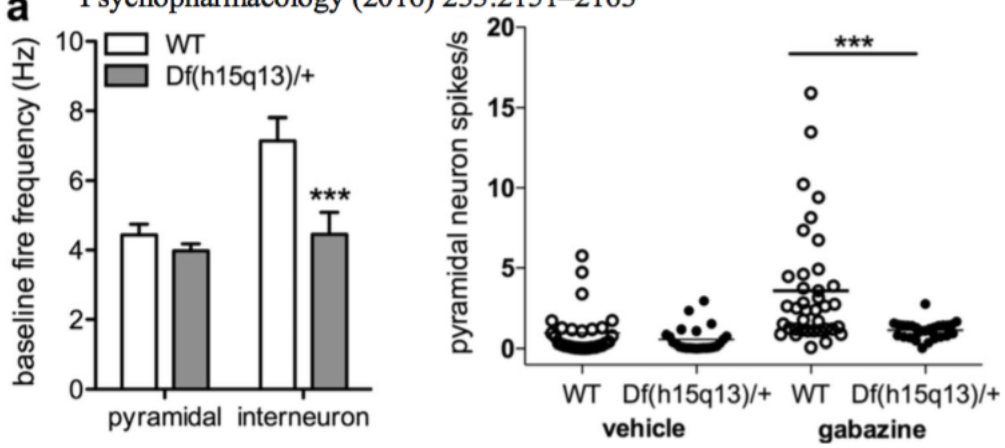
Decreased mPFC-vHipp coherence



22q11.2
Lower FC with cingulate cortex, ectorhinal cortex/perirhinal cortex

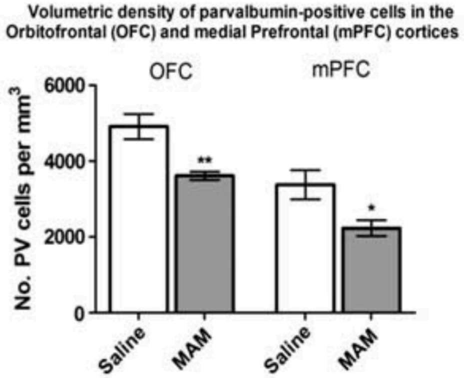
Reduced Hipp-mPFC resting state connectivity

Psychopharmacology (2016) 233:2151–2163

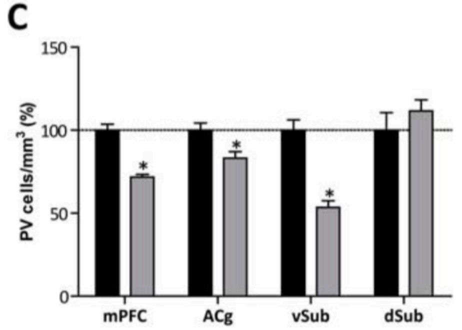


Decreased mPFC PV-interneuron activity /responsivity

Neuropsychopharmacology (2012) 37, 1057–1066



The Journal of Neuroscience, February 25, 2009 • 29(8):2344–2354



Decreased mPFC PV-interneuron expression

ESTABLISH CAUSATIVE/CORRELATIONAL LINKS IN ROBUST, AUTOMATED, REPEATABLE BEHAVIOURAL PARADIGMS

CONCLUSIONS

Lax data interpretations / exp. designs has allowed behavioural effects to become cognitive phenotypes

Sensitive automated systems exist that for detection of ”true” reproducible cognitive phenotypes

These systems should be exploited for :

- Drug discovery against stable performance deficits
- Combined with more sophisticated models and manipulations