Assessing the mouse model of 22q11.2 microdeletion syndrome for cognitive translational potential

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22q11.2 microdeletion syndrome

- Hemizygotic deletion of ≥16 genes at loci 22q11.2

DGCR6	***GNB1L***
PRODH	***TBX1***
RANBP1	***GP1BB***
T10	***PNUT1***
ARVCF	***CLDN5***
COMT	***CDC45L***
TXNRD2	***UFD1L***
	NLVCF
	HIRA

- Biggest known genetic risk factor of schizophrenia (Odds ratio ≈ 30).
  (Stefansson et al. 2008 Nature).

- Associated with autism, ADHD, OCD, depression
  (Schneider et al. 2014 *Am J Psychiatry)*

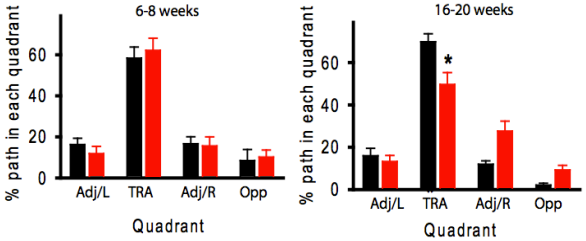
- Carriers show extensive cognitive impairment
  (Stefansson et al. 20014 Nature)

22q11.2DS mouse models

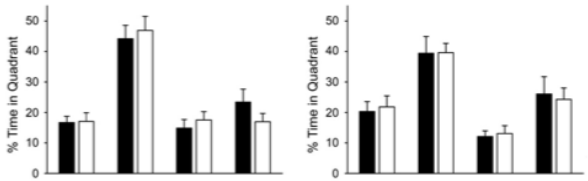
Model	Deletion	Background	Ref.
Df(h22q11)/+	Dgcr2-Hira	C57/Bl6NTac	Fejgin et al. in prep
Df(16)1/+	Dgcr2-Hira	C57/Bl6J	Paylor et al. 2001
Df(16)A$^{+/-}$	Dgcr2-Hira	C57/Bl6J	Stark et al. 2008
LgDel	Dgcr2-Hira	C57/Bl6N	Merscher et al. 2001
Df1/+	Dgcr14-Ufd1l	Mixed C57/Bl6$^{c-/c-}$;129S5/SvEvBrd	Lindsay et al. 1999
	Znf74-Ctp	129SvEvTac *or* mixed 129SvEvTac ; Crl:NIHBL(S)	Long et al. 2006

Reports on cognition in 22q11.2DS mouse models

Water maze

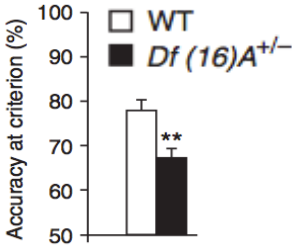


Earls et al. 2010 J Neurosci

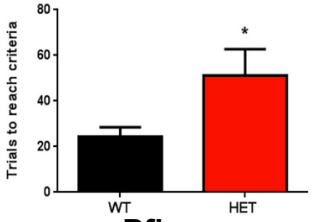


Drew et al. 2011 Mol Cell Neurosci

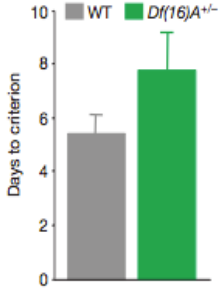
T-maze



Stark et al 2008 Nat Gen



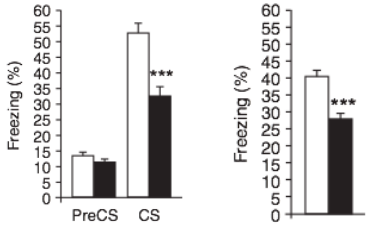
Pfizer – SIRC 2014 Florence



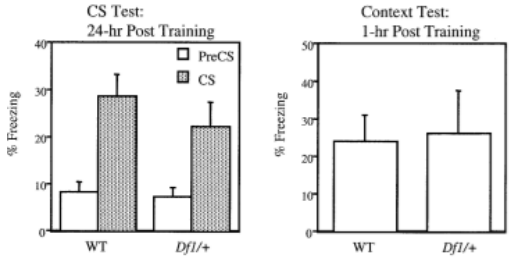
Sigurdsson et al 2010 Nat Let

+ 2-3 SfN posters

Fear-conditioning



Stark et al. 2008 Nat Gen



Paylor et al. 2001 Hum Mol Gen

Some inconsistent reports on cognition in 22q11.2 mouse models
Replicated impairment in 'spatial working memory'

Behavioural assays in 22q11.2 TG

Memory / motivation

- Water maze < 20 weeks
- Water maze > 20 weeks
- Auditory cue fear conditioning
- Paired associate learning
- Novel object recognition
- Visual discrimination
- TUNL – pattern separation
- Progressive ratio

Oomen et al. 2013
Nat Protocols

Working memory

- Y-maze spontaneous alternation
- TUNL – delay challenge
- Radial arm maze
- T-maze – acquisition / delay challenge

Horner et al. 2013
Nat Protocols

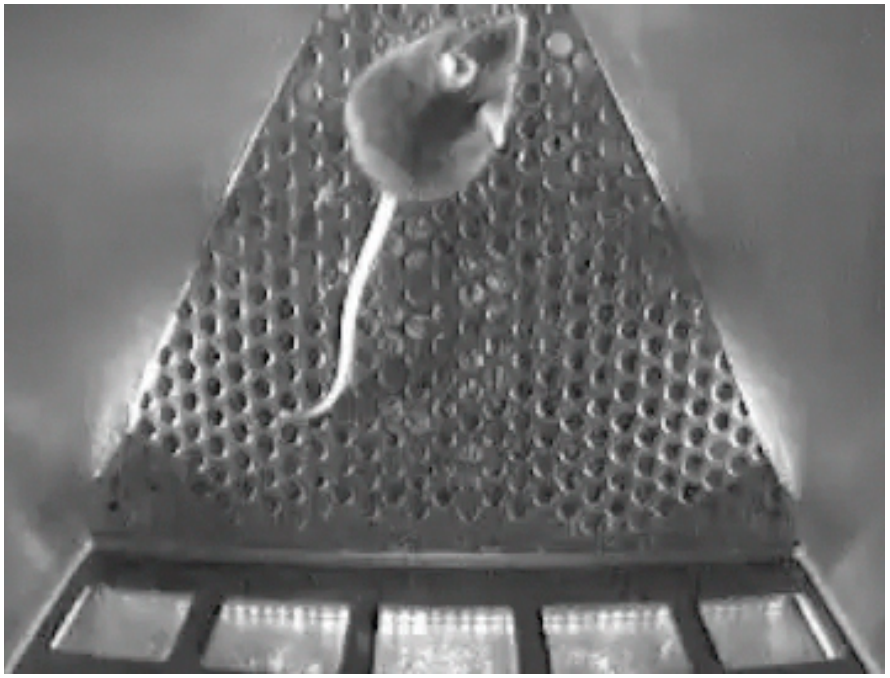
Attention / Executive functioning

- Psychomotor vigilance task
- 5-CSRTT
- Extinction learning
- Reversal learning
- CPT

Mar et al. 2013
Nat Protocols

Touchscreen tasks

5-choice serial reaction time task (UCAM)



Task manipulations

Stimulus duration (*attention*)

Delay (*impulsivity*)

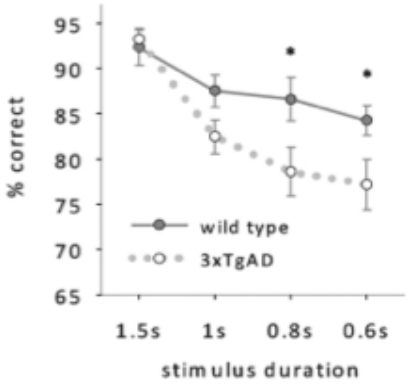
Session length (*sustained attention*)

Main performance measures

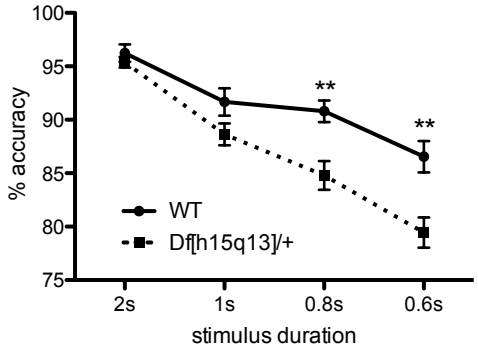
% accuracy (correct / (correct + incorrect))

% omissions (omissions / total trials)

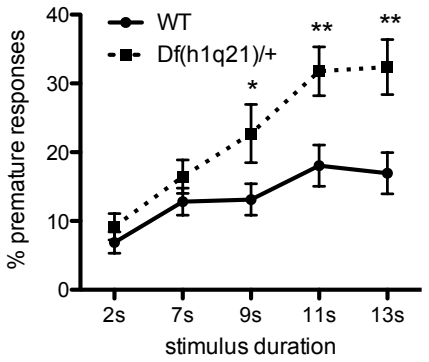
% premature (premature / total trials)



Romberg et al. 2011
J Neurosci



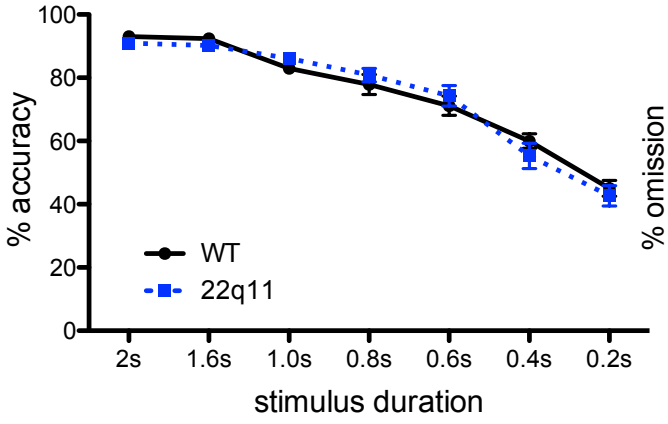
In prep UCAM

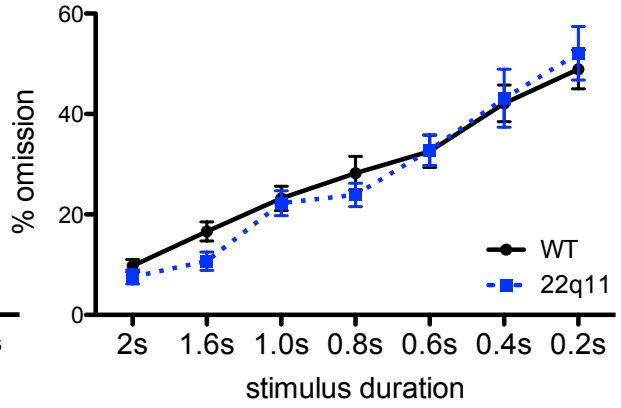


In prep UCAM

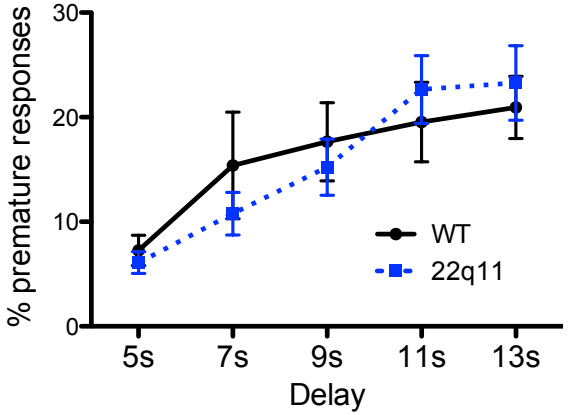
5-CSRTT (UCAM)

Initial tests of decreasing SDs (40 trials / session)

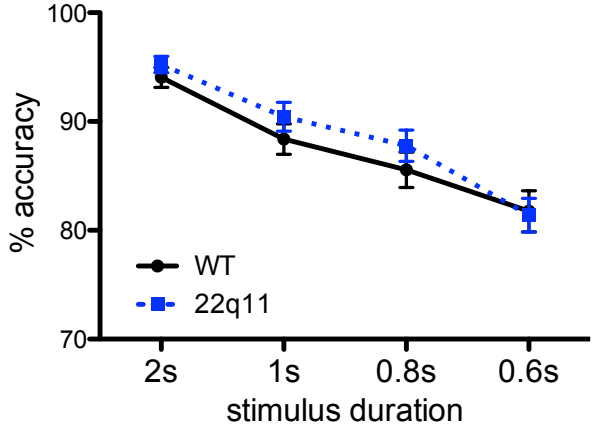


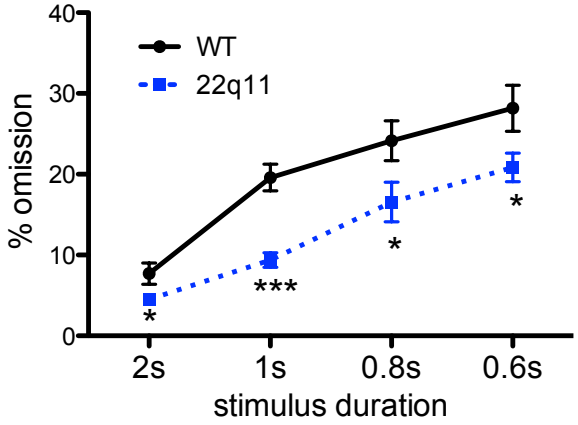


Increasing delays



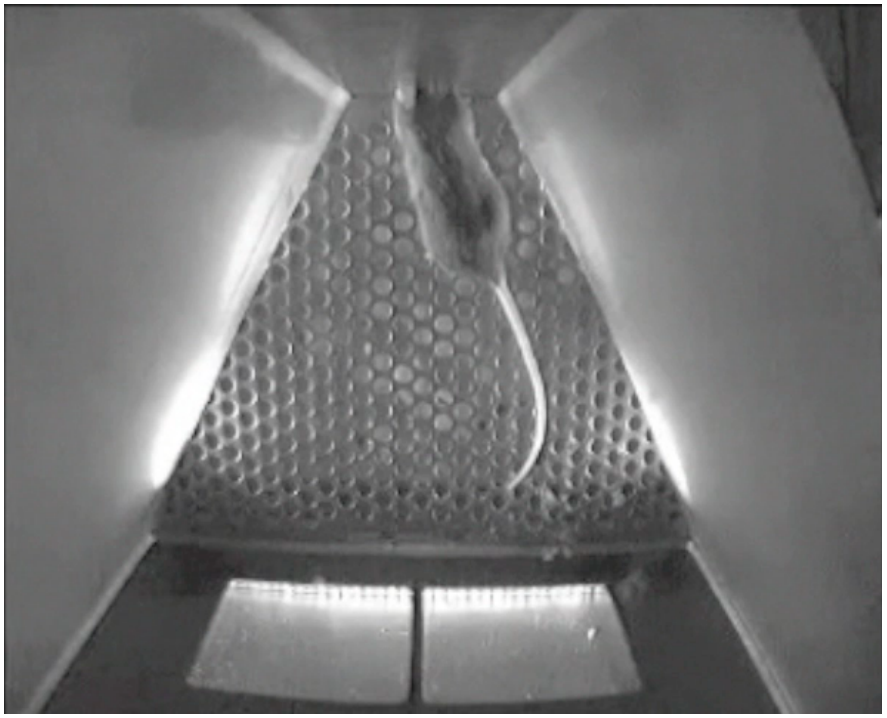
Extended training (100+ sessions, 140 trials / session)





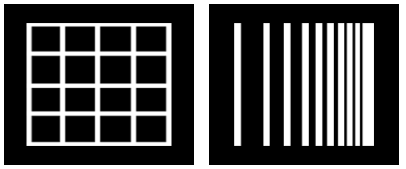
Decreased omissions in TG after extended training

Visual discrimination and reversal learning



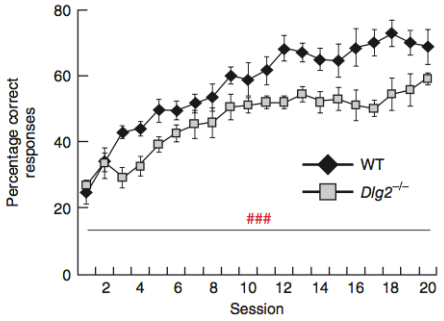
Two discriminations and reversals

‘Easy’

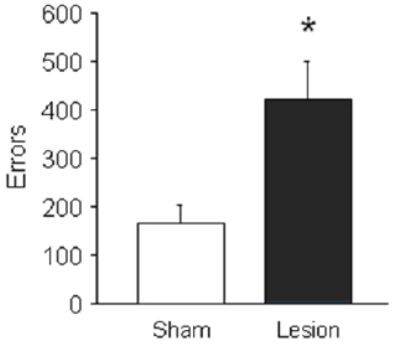


‘Difficult’

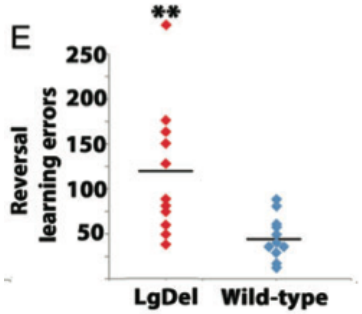
Criterion = 24 / 30 correct × 2



Nithianantharajah et al. 2013
Nat Neuroscience



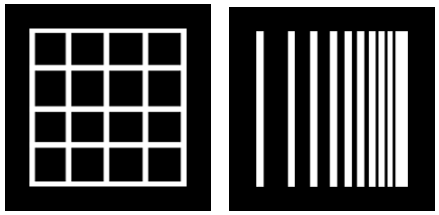
Graybeal et al. 2011
Nat Neuroscience

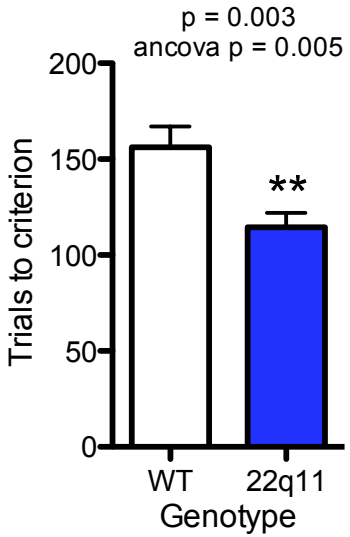


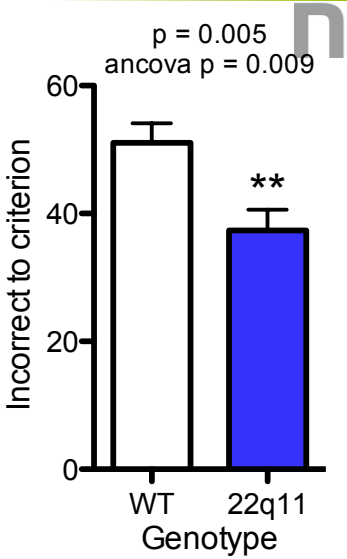
Meechan et al. 2013
Cerebral Cortex

Reversal learning (UCAM)

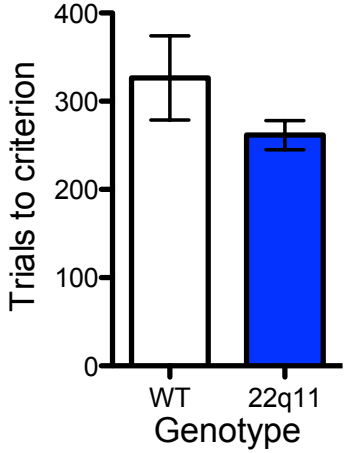
‘Easy’

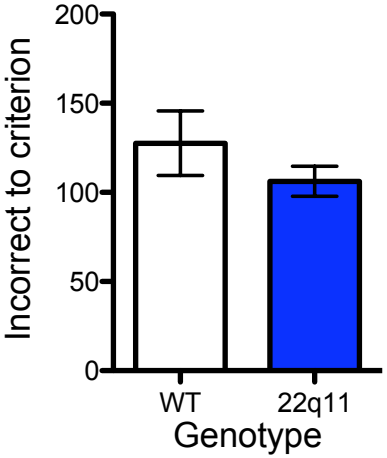






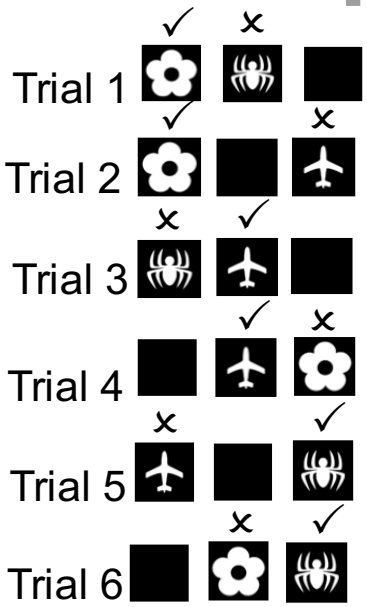
‘Difficult’

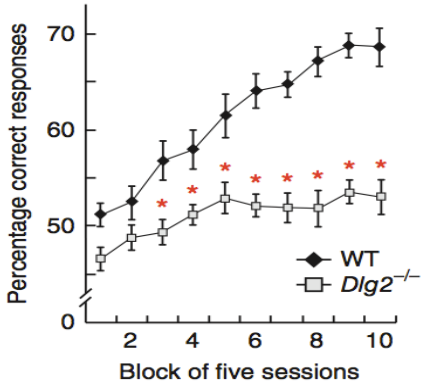




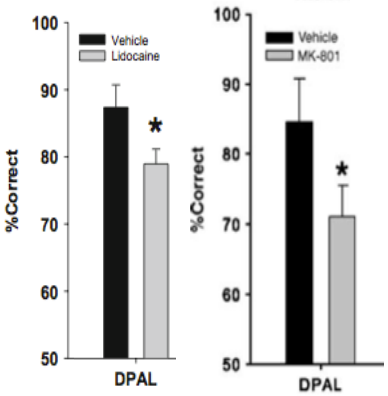
The 22q11 TG show improved ‘easy’ VD / REV
No effects in a 2nd ‘difficult’ VD / REV

Rodent paired-associate learning (UCAM)

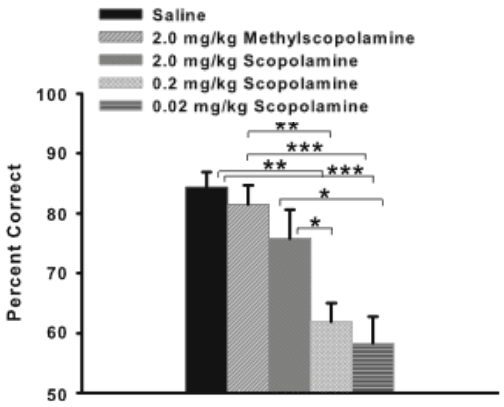




Nithianantharajah et al. 2013
Nat Neuroscience

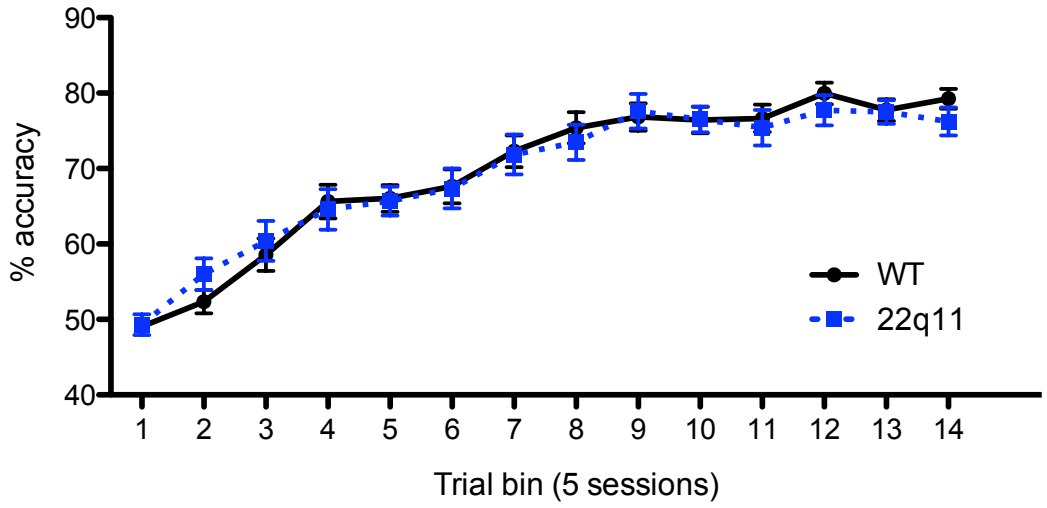


Talpos et al. 2009
Psychopharm



Bartko al. 2011
Psychopharm

Paired-associate learning (UCAM)



No effect of genotype on PAL

Touchscreen non-match to sample (UCAM)

Test of working memory

Sample phase

Delay
Baseline: 2s
Probes: 4s, 6s and 8s

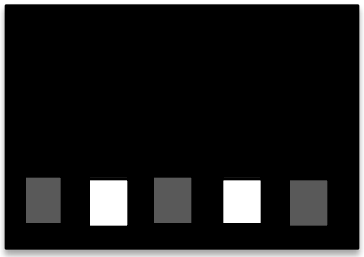
Test phase

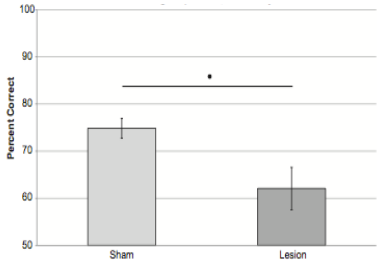
Test of pattern separation

Sample phase

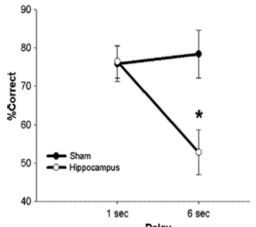
Delay (2s)

Test phase





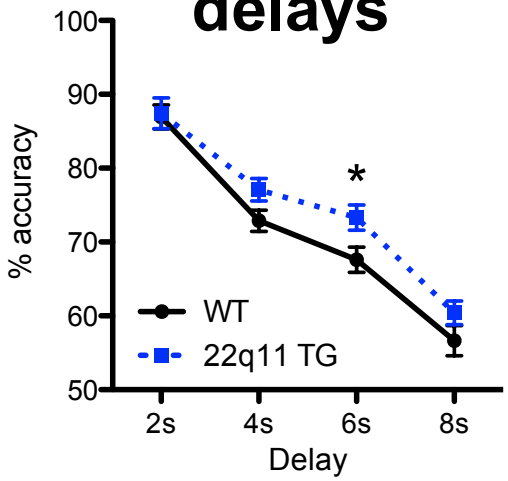
McAllister et al. 2013
Neurobiol Learn Mem

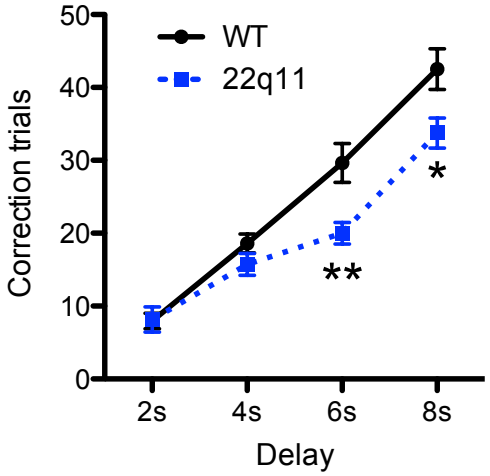


Talpos et al. 2010
Neurobiol Learn Mem

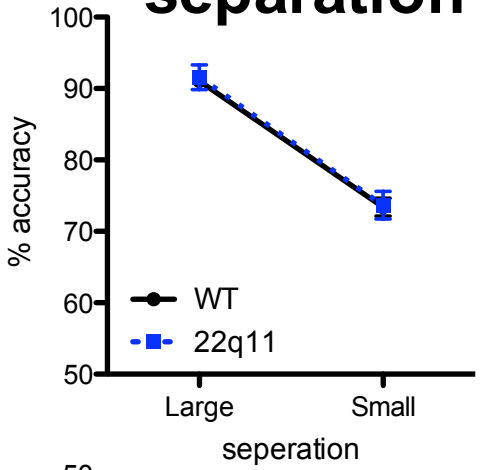
Mouse TUNL (UCAM)

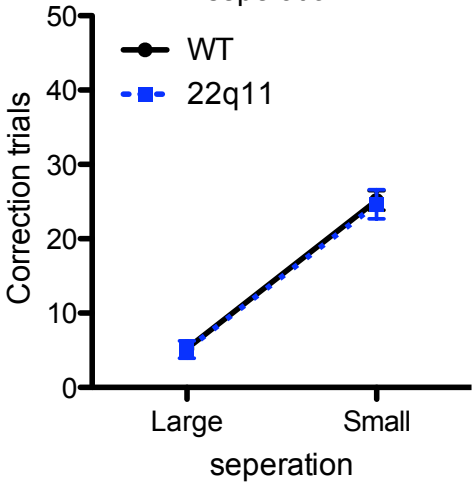
Manipulating delays





Manipulating separation

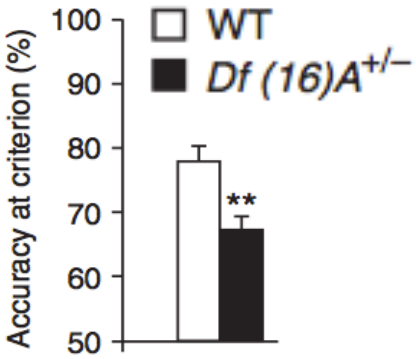




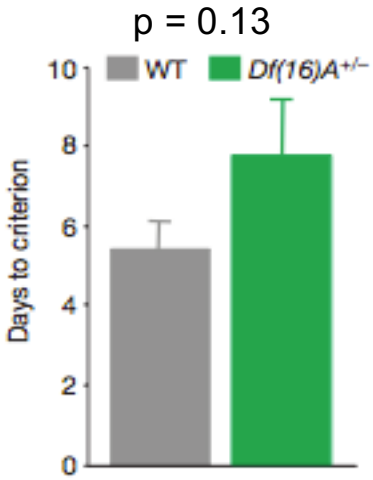
Sig. delay-dependent improvement in the TG on TUNL

Traditional behavioural tasks

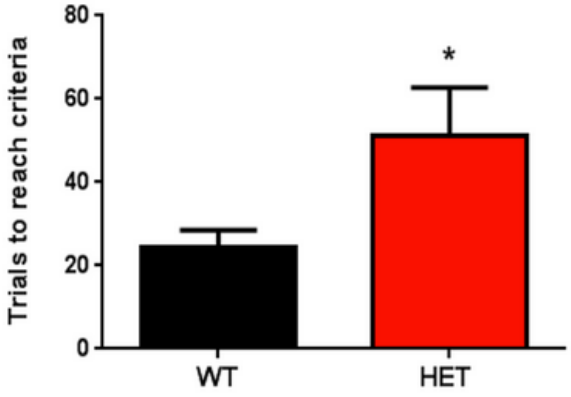
T-maze – reports from alternative 22q11 models



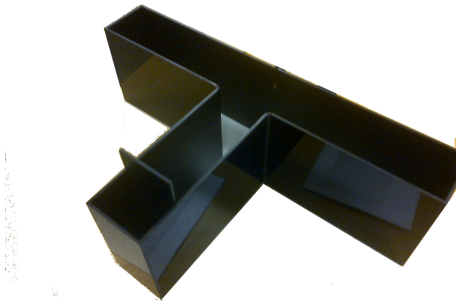
Stark et al 2008
Nature Genetics



Sigurdsson et al 2010
Nature Letters



Zoe Hughes et al.
Pfizer – SIRC 2014 Florence



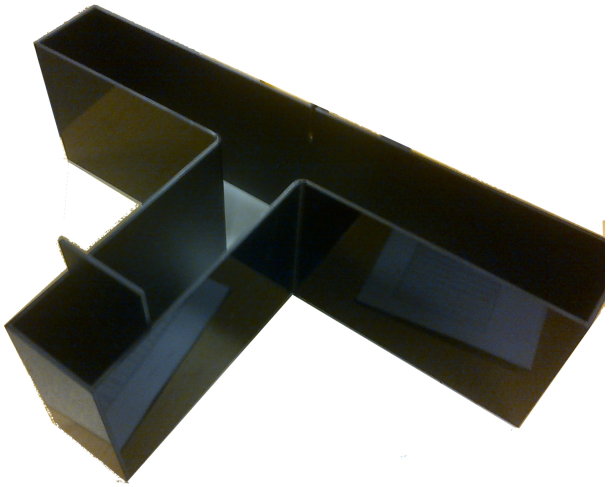
Acquisition impairments in 22q11 mouse models on T-maze spatial alternation.

No reports of performance at longer delays.

T-maze (UCAM)

Group-housed (N = 20)

Single-housed (N = 25)



Pre- training

2 days of forced alternation

Task acquisition

10 trials / session using 10s delay

Criterion = 7 / 10 correct x 3 consecutive session

Working memory test using variable delays

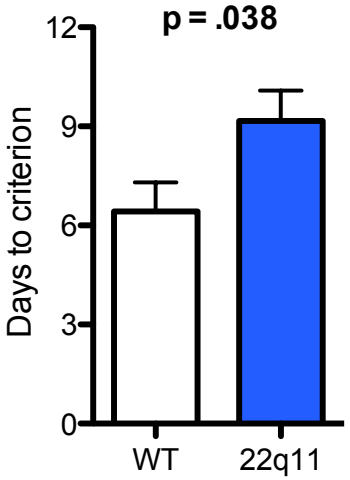
4 sessions of 12 trials

Variable delays: 10s, 60s, 120s, 240s

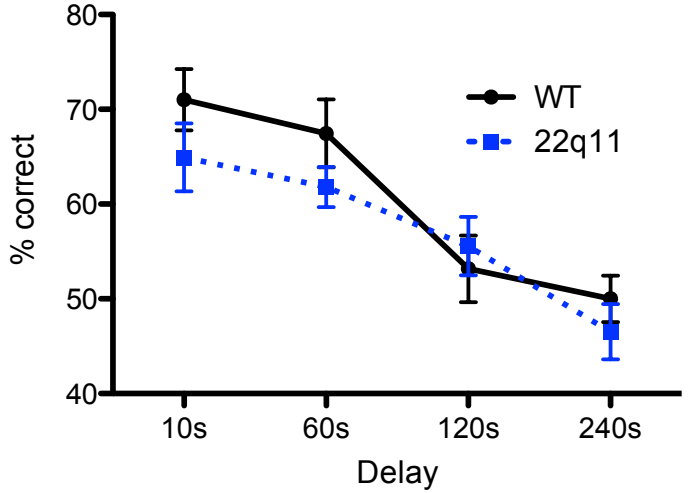
Additional test on 3 session of 12 trials at variable delays 10s and 90s (Single-housed)

T-maze – UCAM

Acquisition



Variable delays



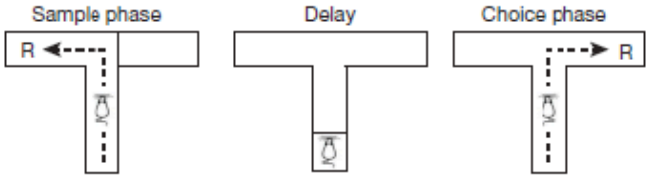
Impaired T-maze alternation acquisition

No effect of genotype at longer delays

No effect of housing condition

Automated T-maze (Lilly)

Animals
Df(h22q11)/+, male, 7 months old
13 WT, 16 22q11



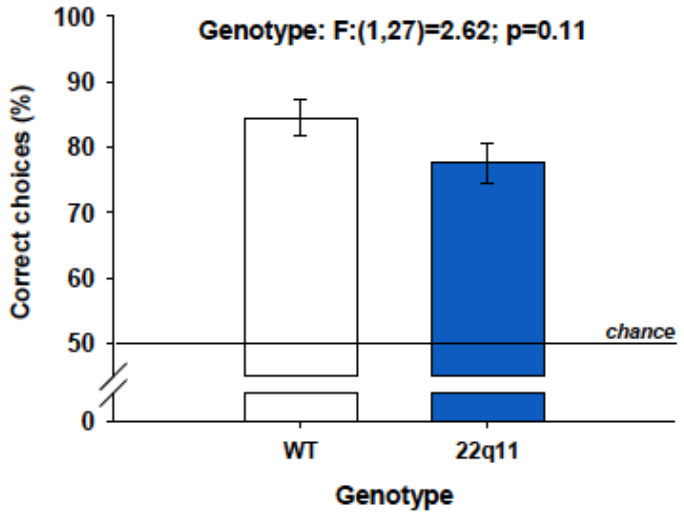
Automated T-maze
Delayed non-matching to place
Spatial working memory task

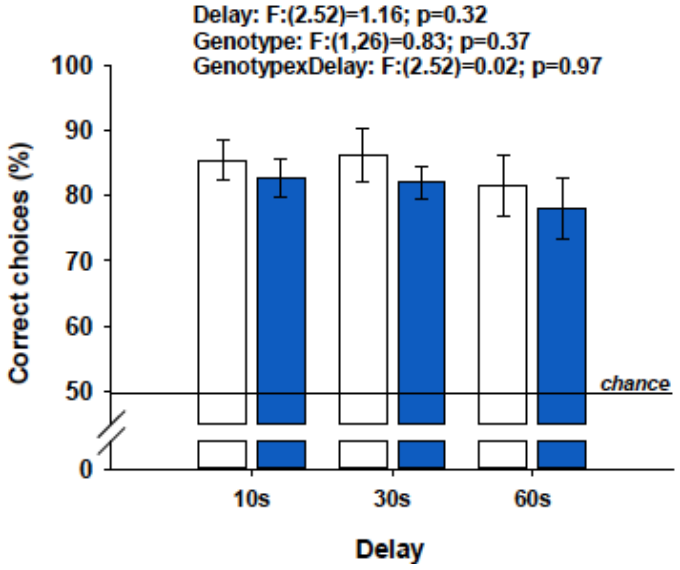
Protocol (1)
1 day, 1 hour or 20 trials
1 trial = sample phase and test phase
IPI = 10s, ITI = 30s
Left and right locations were counterbalanced (max of 3 in a row)

Protocol (2)
2 days, 15 trials per day (5 trials per delay)
1 trial = sample phase and test phase
IPI = 10, 30 or 60s, ITI = 30s
Left, right locations and delays were counterbalanced (max of 3 in a row)

Results (1)
No genotype effect neither in the number of trials nor in choice accuracy.

Results (2)
No genotype, delay or genotype*delay effect.





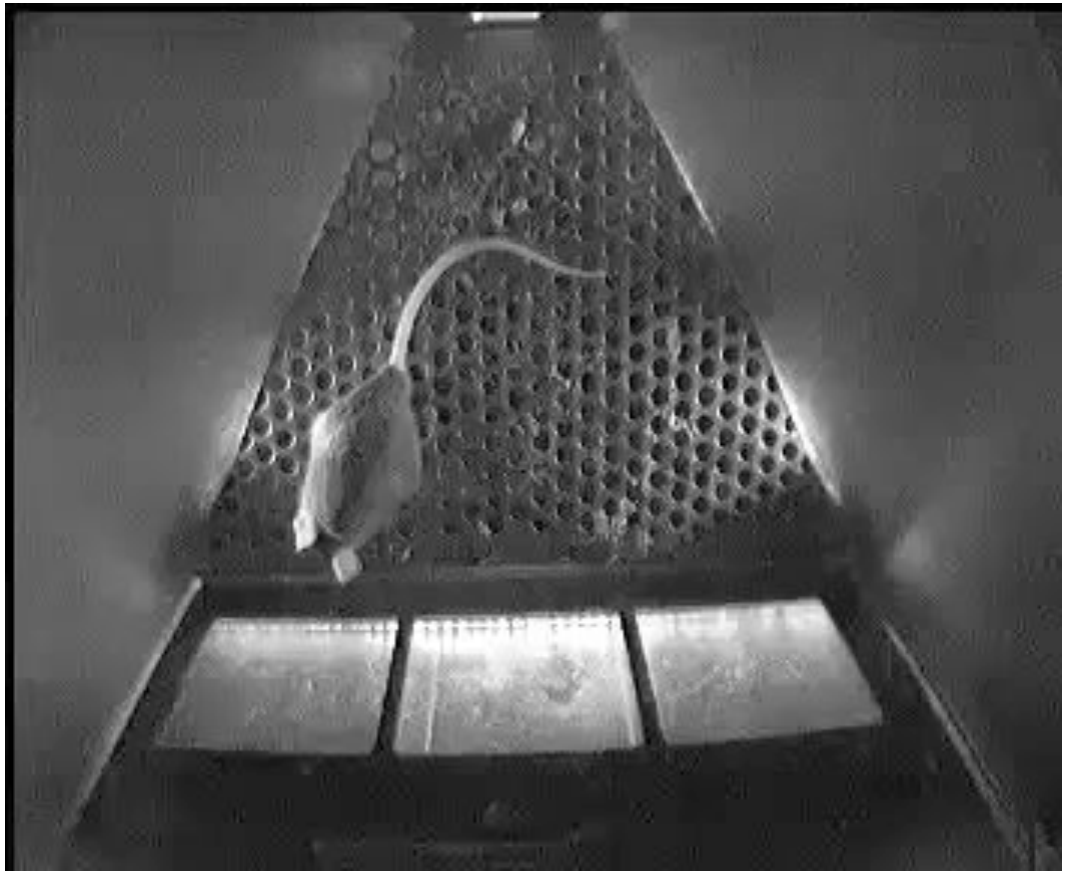
No significant effects of genotype in the automated T-maze

Summary

Model		Df(h22q11)/+	Df(16)1/+	Df(16)A$^{+/-}$	LgDel	Df1/+	
Deletion		Dgcr2-Hira	Dgcr2-Hira	Dgcr2-Hira	Dgcr2-Hira	Dgcr14-Ufd1l	Znf74-Ctp
Strain		C57/Bl6NTac	C57/Bl6J	C57/Bl6J	C57/Bl6N	Mixed C57/Bl6$^{c-/c-}$;129S5/SvEvBrd	129SvEvTac *or* mixed 129SvEvTac ; Crl:NIHBL(S)
Behaviour	**Paradigm**						
Memory	Water maze < 20 weeks	×	×[26]	-	-	-	-
	Water maze > 20 weeks	×	↓[26]	×	-	-	-
	Contextual fear conditioning	×		↓[19]	×[25]	↓[22]	×[29]
	TUNL – pattern separation	×	-	-	-	-	-
	Auditory-cue fear conditioning	×		↓[19]	×[25]	×[22]	×[29]
	Touchscreen PAL	×	-	-	-	-	-
	Novel object recognition	×	-	-	-	-	-
	Touchscreen discrimination learning						
	‘Easy’ discrimination	↑	-	-	-	-	-
	‘Difficult’ discrimination	×	-	-	↓[28]	-	-
Working Memory	Y-maze spontaneous alternation	×	-	-	-	-	-
	TUNL – delay challenge	↑	-	-	-	-	-
	Radial arm-maze	×	-	-	-	-	-
	T-maze non-match to sample						
	Acquisition	↓	↓[24]	↓[19]×[25]	-	-	-
	Delay challenge	×	-	-	-	-	-
Executive function	PVT - Premature responses	×	-	-	-	-	-
	5CSRTT - Premature responses	×	-	-	-	-	-
	Touchscreen extinction learning	×	-	-	-	-	-
	Touchscreen reversal learning						
	‘Easy’ reversal	↑	-	-	-	-	-
	‘Difficult’ reversal	×	-	-	↓[28]	-	-
Attention	PVT - Reaction time	×	-	-	-	-	-
	PVT - Correct responses	×	-	-	-	-	-
	5-CSRTT - Accuracy	×	-	-	-	-	-
	5-CSRTT - Omissions	↑	-	-	-	-	-

Table 1. Cognitive functioning in the Df(h22q11)/+ mutant and other 22q11.2DS mouse models. ↓ impaired, ↑ improved, × no effect, - no data.

Continuous Performance Task (UCAM)



Task manipulations

Stimulus duration

Session length

Inter-trial interval

Event rate

Stimulus contrast

Main performance measures

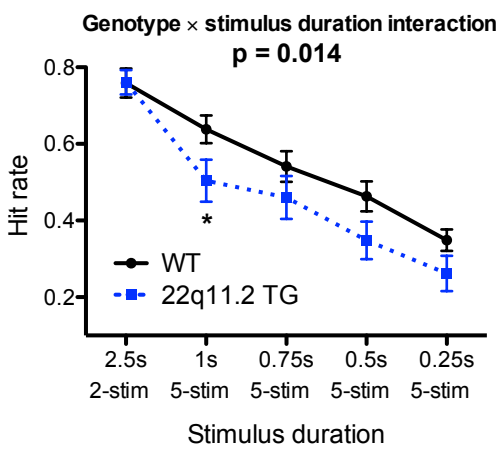
Hit rate = Correct / (Correct + Misses)

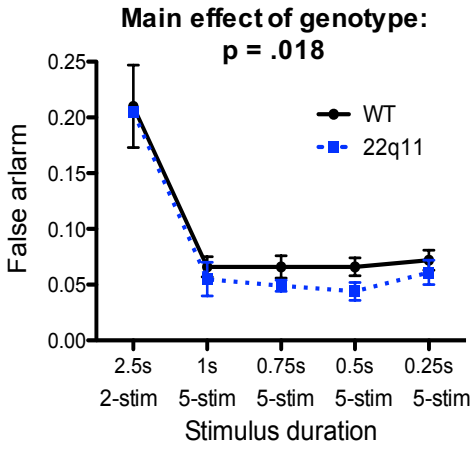
False alarm rate = Mistakes / (Mistakes + Correct rejections)

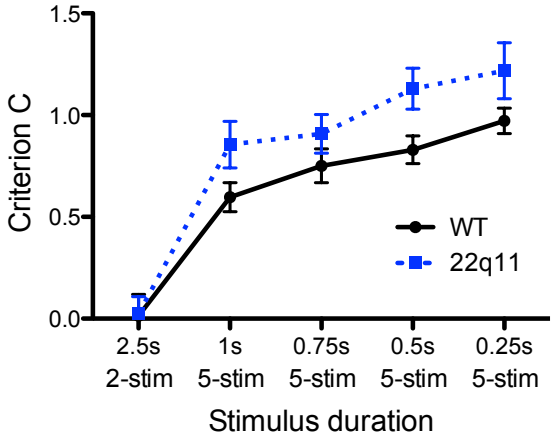
Criterion C =

Continuous Performance Task (UCAM)

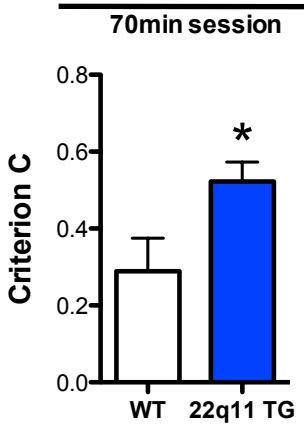
Stimulus duration



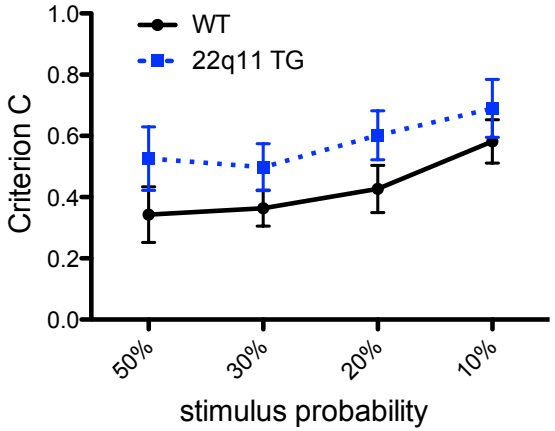




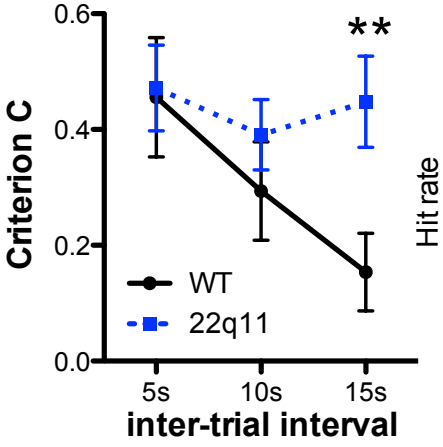
Session length



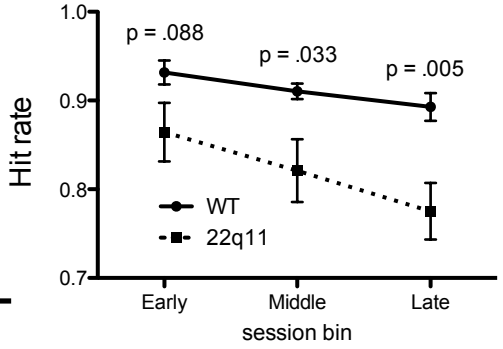
CS+ probability



ITI



Replication



Summary and outstanding questions

- **Few impairments useful for drug-discovery**
  No impairments in published operant tasks and no robust deficits in traditional tasks

- **Robust replicable attentional impairment in the rodent CPT task**

- Few test of the causative mechanisms underlying vigilance in automated tasks
- No assessments of mechanisms underlying cognitive impairment in 22q11.2 model
- No reports of use of DREDDs in touchscreen tasks
- No set-up for optogenetic manipulations in touchscreen tasks exist

Tentative plans

- Touchscreen set-up for optogenetic manipulations in mice
- Use this to investigate the role of mPFC circuitry in attention
  - **Inihibition:** Light targeted at the mPFC of PV-Cre mice with mPFC-AAV-ChR2
  - **Excitation:** Light targeted at the mPFC of αCamKII-Cre mice with mPFC-AAV-ChR2
- Probe the role of the mPFC in attentional impairment in 22q11.2 TG
  - **Create** PV-Cre or αCamKII-Cre Df(h22q11)/+ mice with mPFC-specific ChR2
  - **Central** pharmacological infusions in Df(h22q11)/+