Assessing the mouse model of 22q11.2 microdeletion syndrome for cognitive translational potential: a multi-site study

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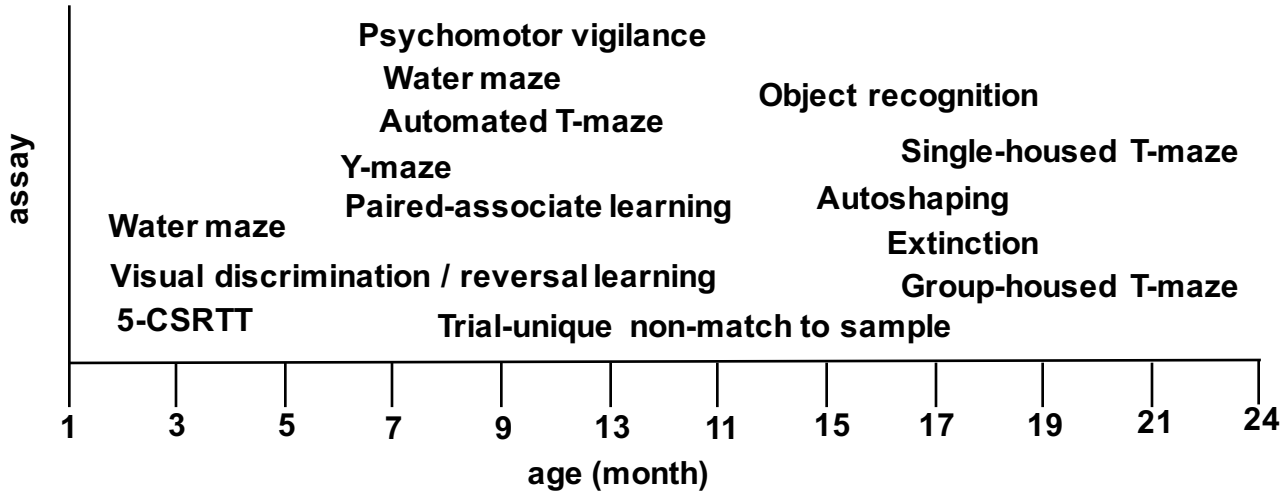
Target journal: Molecular Psychiatry

Cognitive assays in the 22q11 transgenic

✧ Water maze	*Lundbeck*
✧ Novel object recognition	*UCAM*
✧ Psychomotor vigilance	*Lilly*
✧ Cue / Context fear conditioning	*Lundbeck*
✧ T-maze Columbia protocol	*UCAM*
✧ Automated T-maze	*Lilly*
✧ Y-maze spontaneous alternation	*Lilly*
✧ Touchscreen visual discrimination / reversal	*UCAM*
✧ Touchscreen TUNL	*UCAM*
✧ Touchscreen PAL	*UCAM*
✧ Touchscreen 5-CSRTT	*UCAM*
✧ Touchscreen Extinction	*UCAM*
✧ Bowl-digging ID/ED	*ZI Mannheim*
✧ Radial-arm maze	*ZI Mannheim*
✧ Social interaction	*ZI Mannheim*

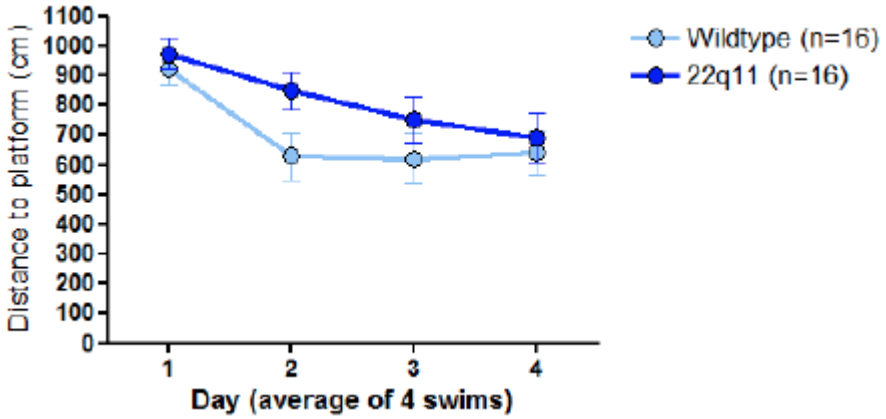
Timeline – assays in 22q11 TGs

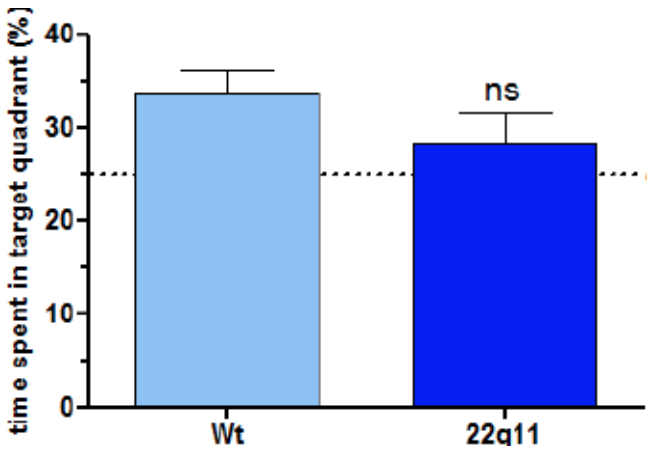


Non-touchscreen assays

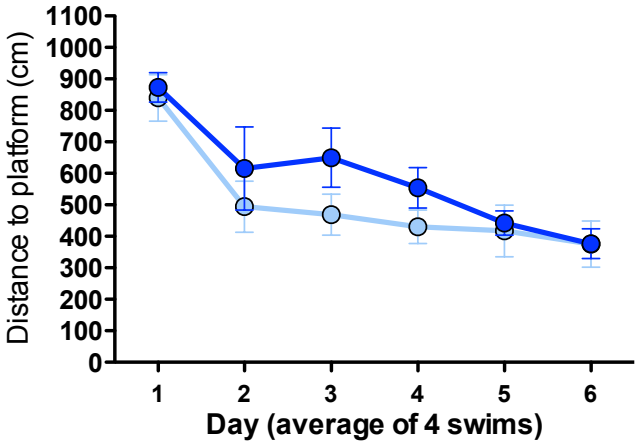
Water maze (Lundbeck)

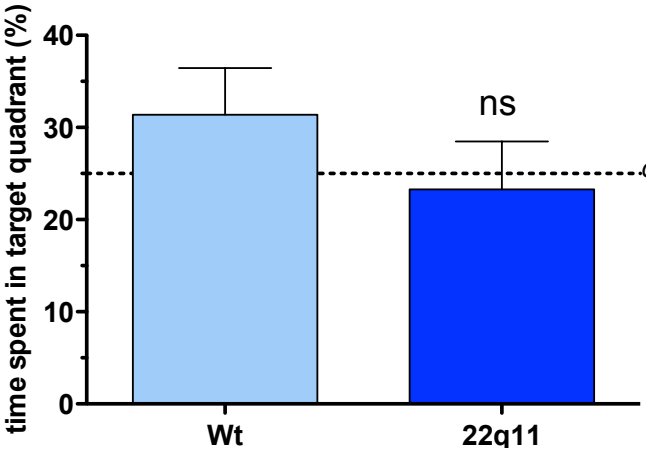
10 week old





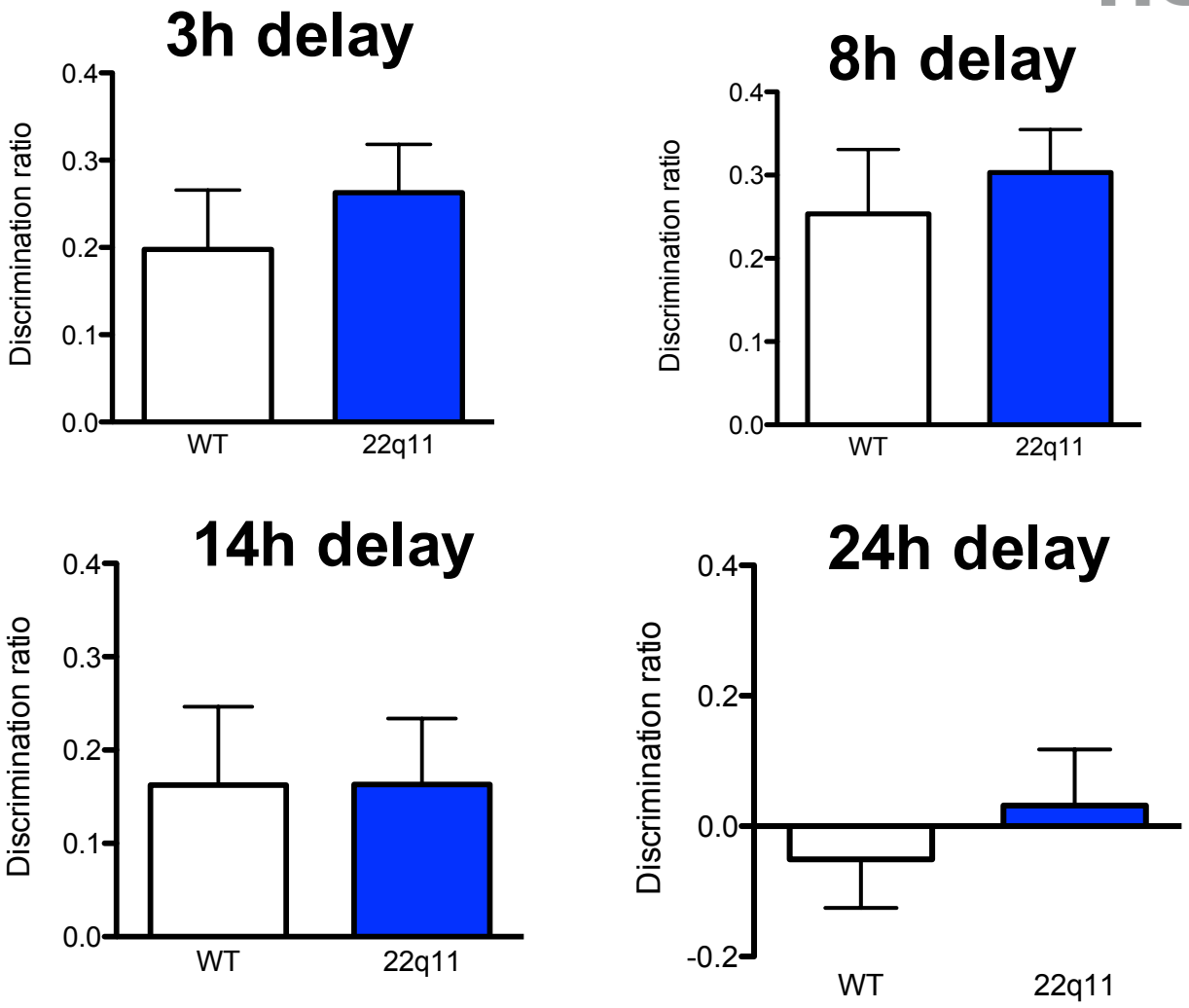
25 week old





No sig. effects of genotype on acquisition and 24h probe in the water maze

Novel object recognition (UCAM)

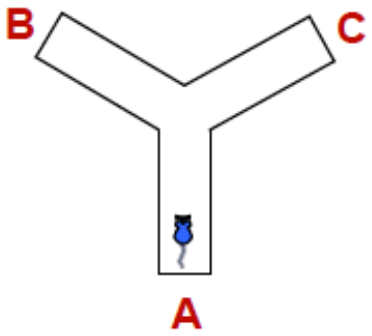


No effect of genotype on object recognition

Y-maze (Lilly)

Animals
Df(h22q11)/+, male, 6 months old
15 WT, 16 22q11

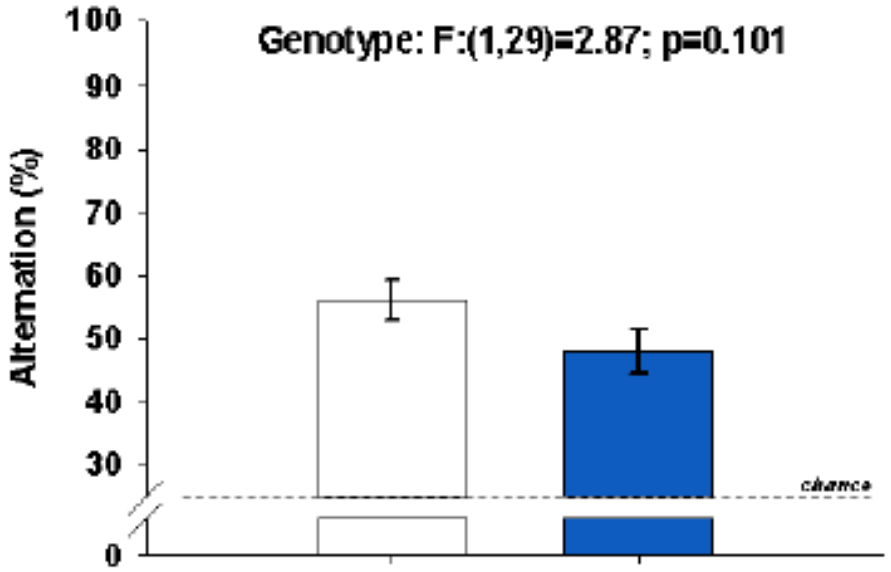
Y-maze
Spontaneous alternation
Spatial working memory task



Protocol
Mice were placed at the end of a pseudo-randomly chosen arm and observed for 15 min. The sequence of arm entries was recorded.

The alternation rate was calculated as the number of complete alternations (ABC, CAB, BCA) divided by the total number of alternation opportunities (total number of arm entries - one).

The chance level is at 22%

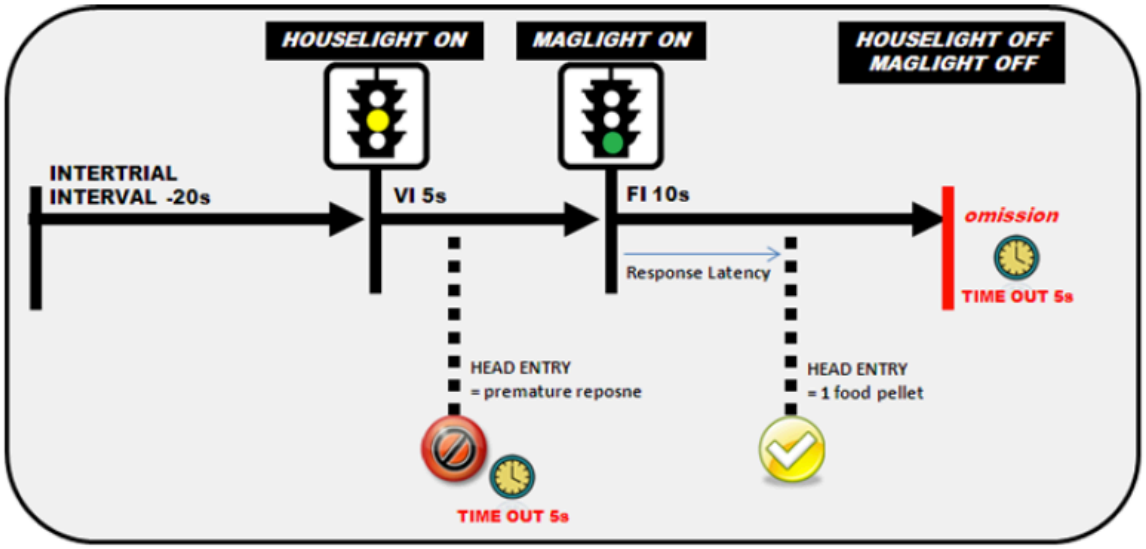


No sig. effect of genotype in the Y-maze

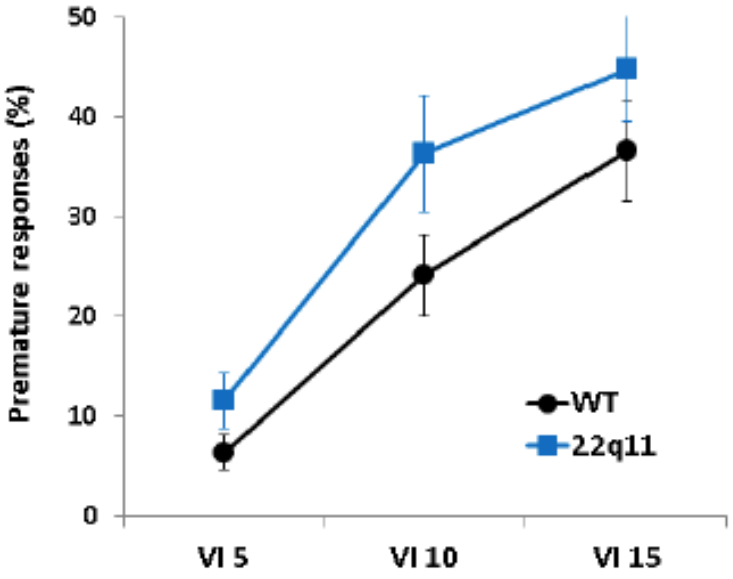
Also observed at Lundbeck

Psychomotor vigilance task (Lilly)

Animals
Df(h22q11)/+, male, 7-9 months old
13 WT, 16 22q11

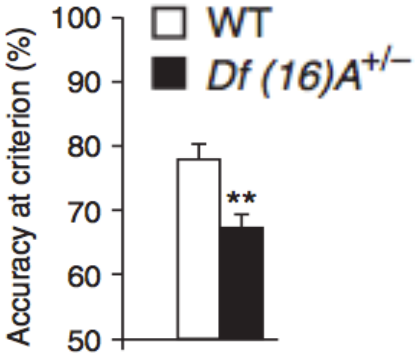


VI: F(2,54)=32.16; p < 0.001
Genotype: F(1,27)=3.8; p = 0.06
Genotype x VI: F(2,54)=0.37; p = 0.69



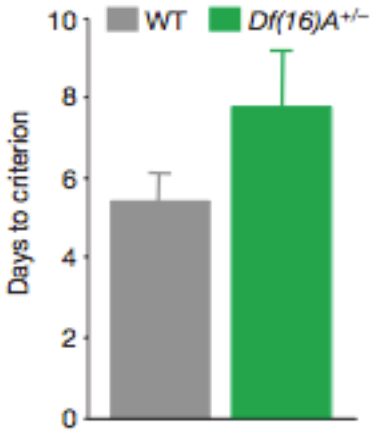
Non-significant trend for the 22q11 TG to make more premature responses

T-maze – reports from alternative 22q11 models

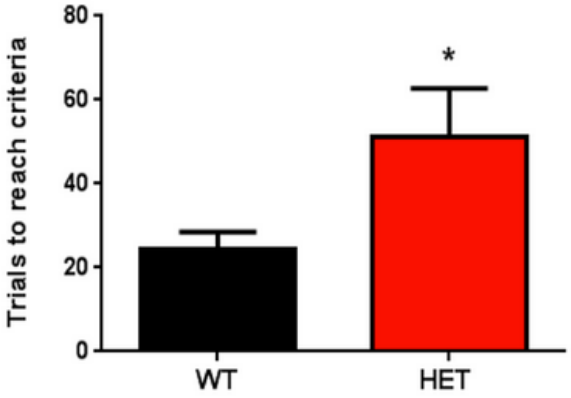


Stark et al 2008
Nature Genetics

p = 0.13



Sigurdsson et al 2010
Nature Letters



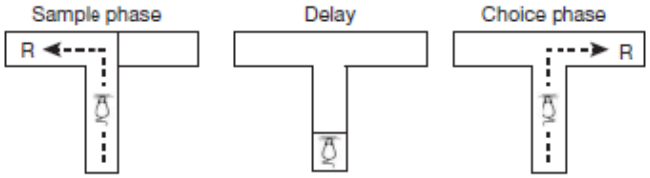
Zoe Hughes et al.
Pfizer – SIRC 2014 Florence

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

No reports of performance at longer delays.

Automated T-maze (Lilly)

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



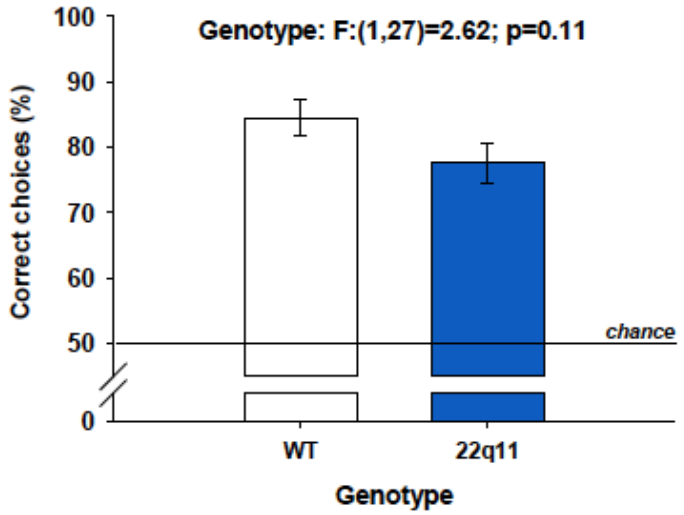
Automated T-maze
Delayed non-matching to place
Spatial working memory task

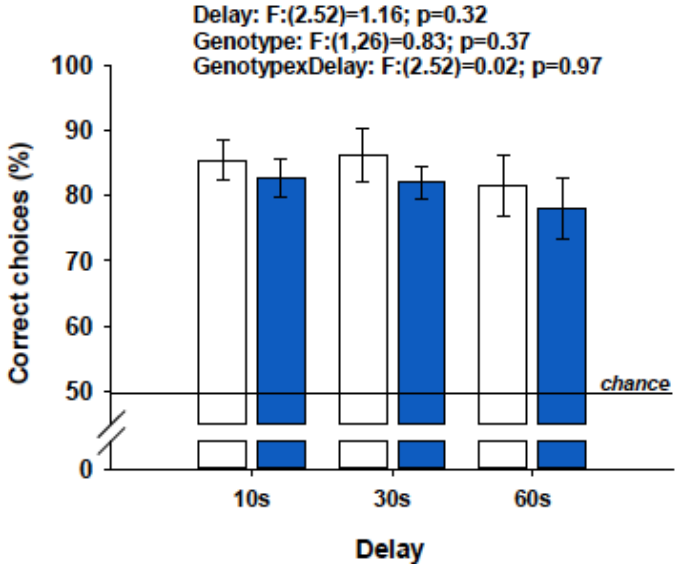
Protocol (1)
1 day, 1 hour or 20 trials
1 trial = sample phase and test phase
IPI = 10s, ITI = 30s
Left and right locations were counterbalanced (max of 3 in a row)

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.



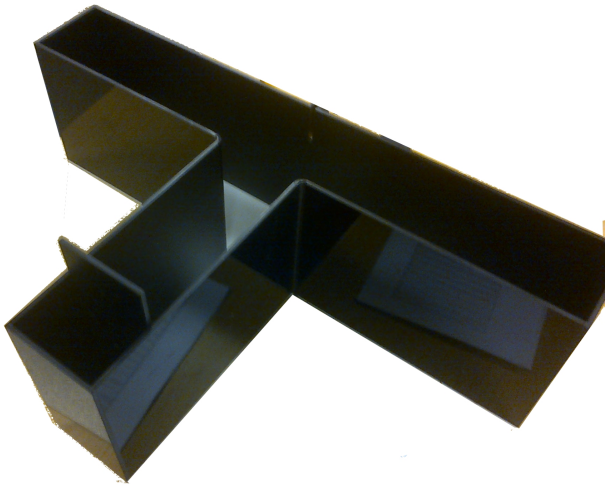


No significant effects of genotype in the automated T-maze

T-maze – 'Columbia' protocol (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

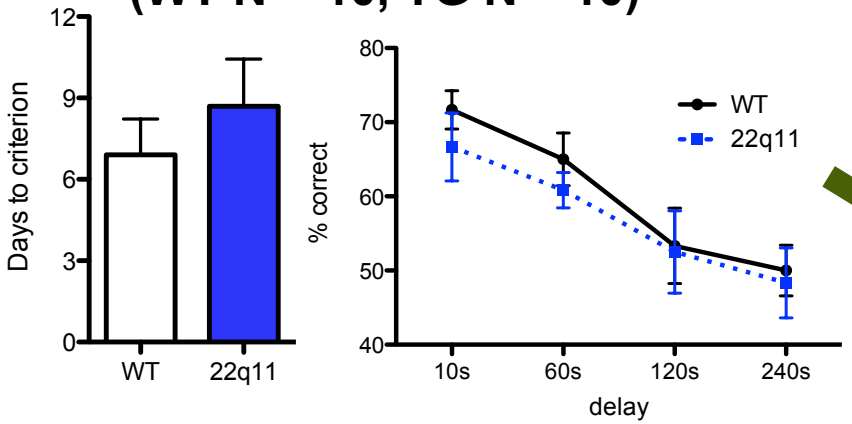
4 sessions of 12 trials

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

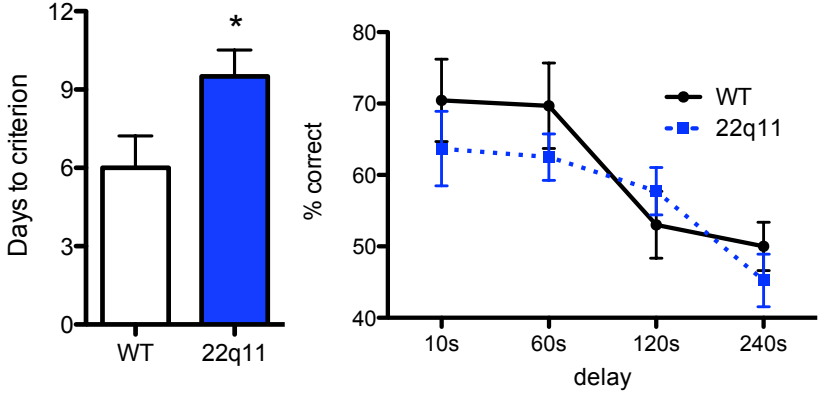
Additional test on 3 session of 12 trials at variable delays 10s and 90s (Single-housed)

T-maze – 'Columbia'-protocol UCAM

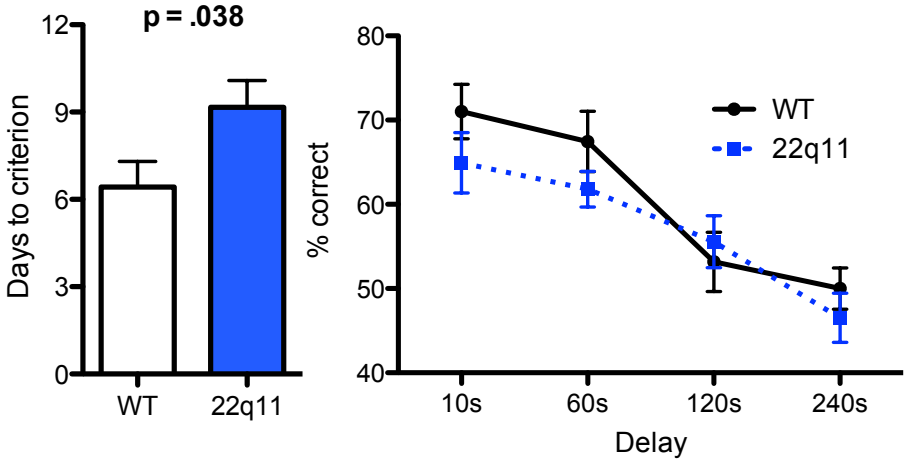
Group-housed (WT N = 10, TG N = 10)



Single-housed (WT N = 11, TG N = 14)



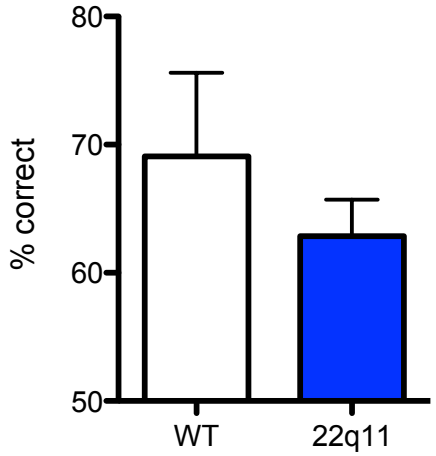
Collapsed (WT N = 21, TG N = 24)



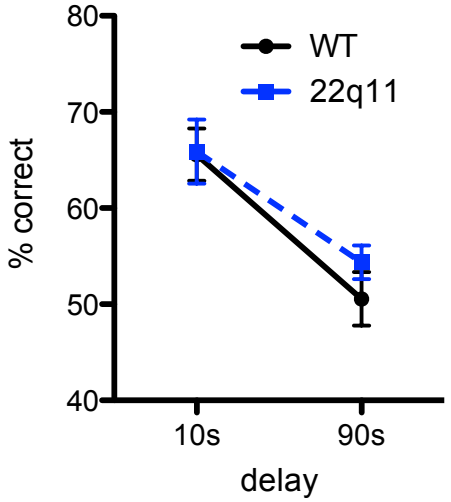
No effect of housing condition on task-performance

T-maze – 'Columbia'-protocol UCAM

1st day of acquisition training
Single-housed



Variable delays
10s vs. 90s

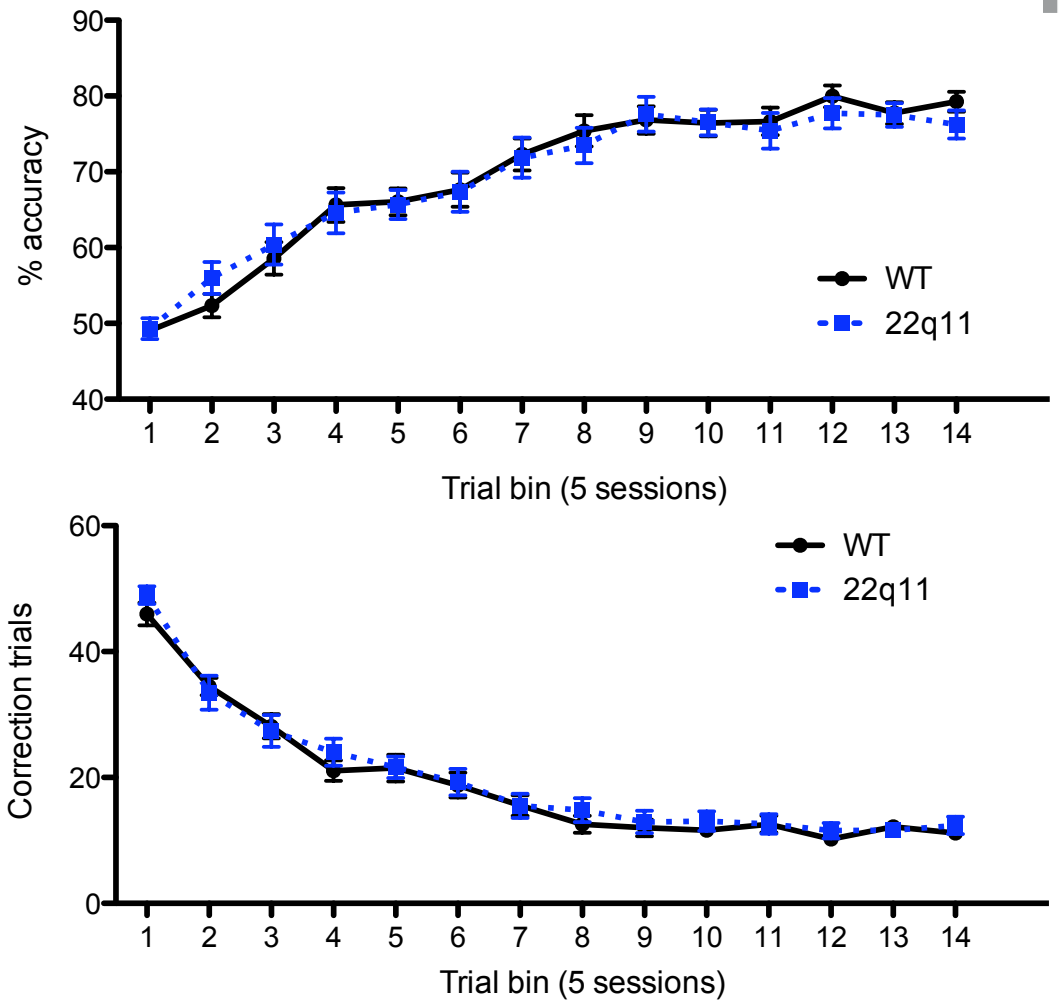


Slight decrease in performance on day 1 in the TG

No effect of genotype at 90s delay

Touchscreen assays

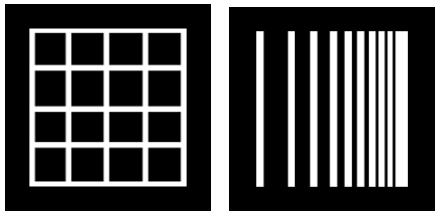
Paired-associate learning (UCAM)

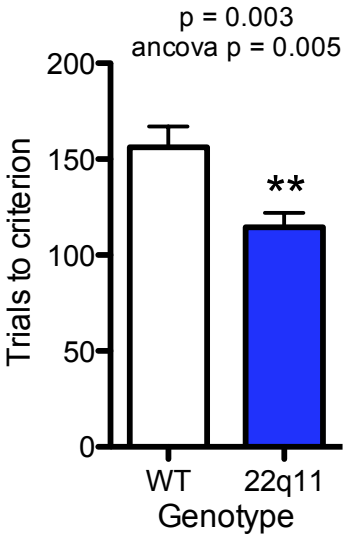


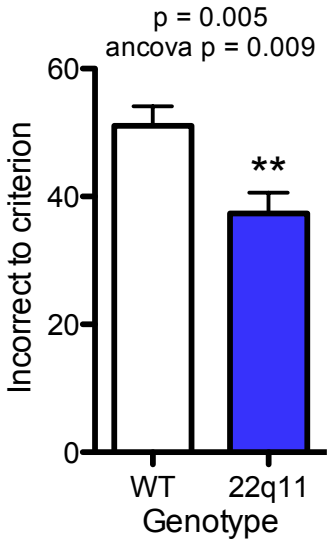
No effect of genotype on PAL

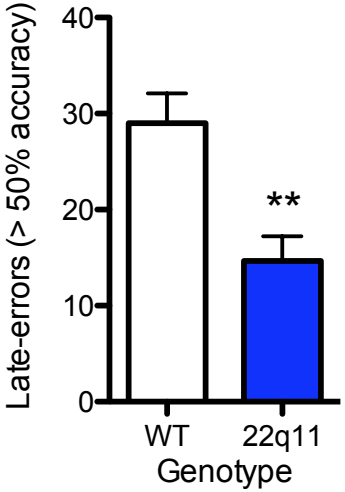
Reversal learning (UCAM)

‘Easy’

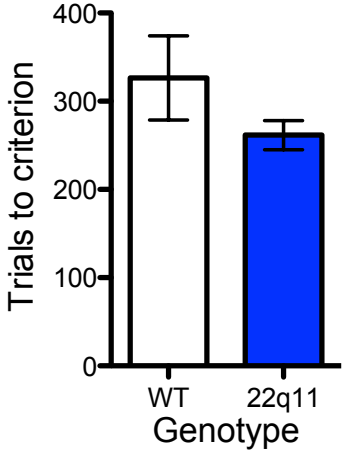


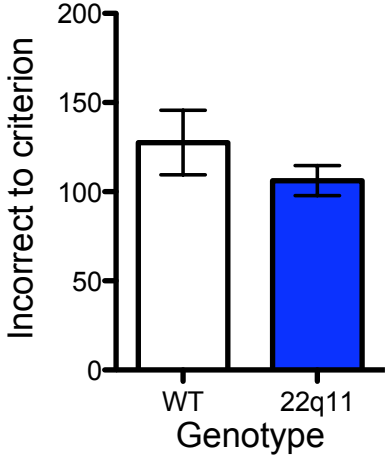


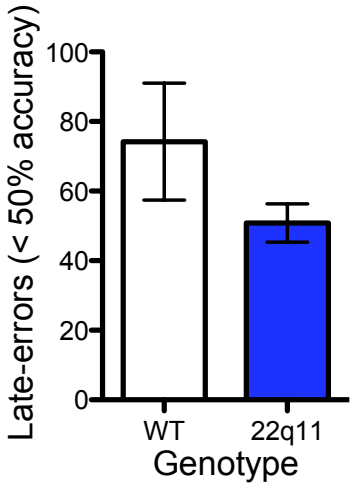




‘Difficult’



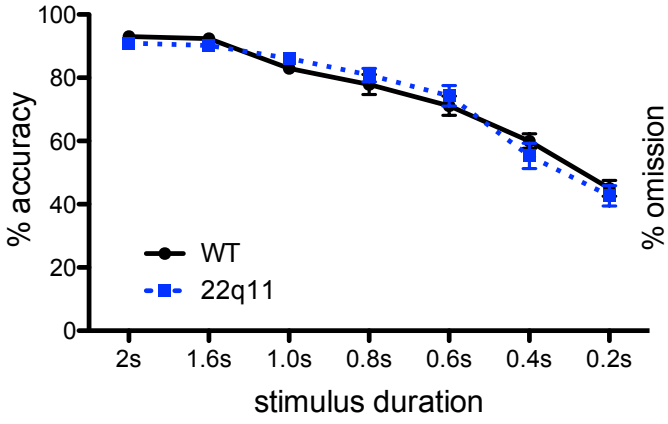


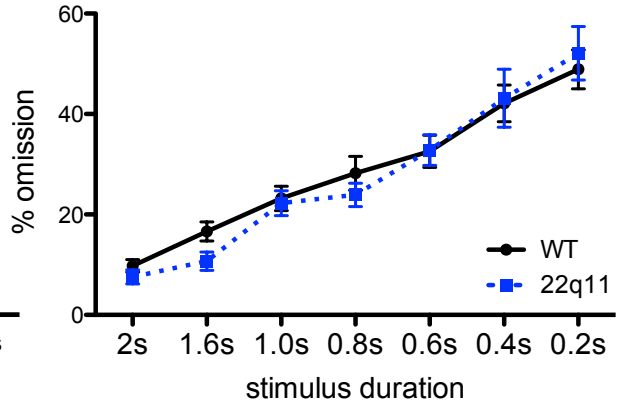


The 22q11 TG show improved ‘easy’ VD / REV
No effects in a 2nd ‘difficult’ VD / REV

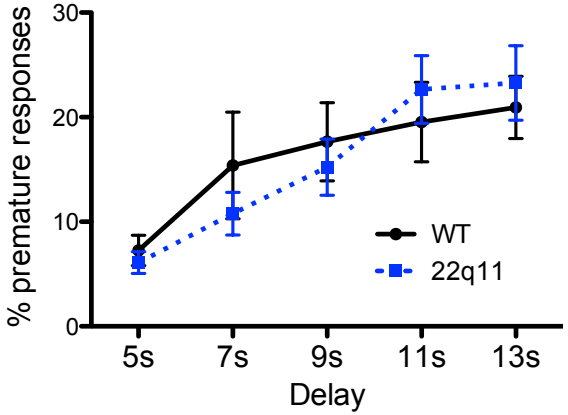
5-CSRTT (UCAM)

Initial tests of decreasing SDs (40 trials / session)

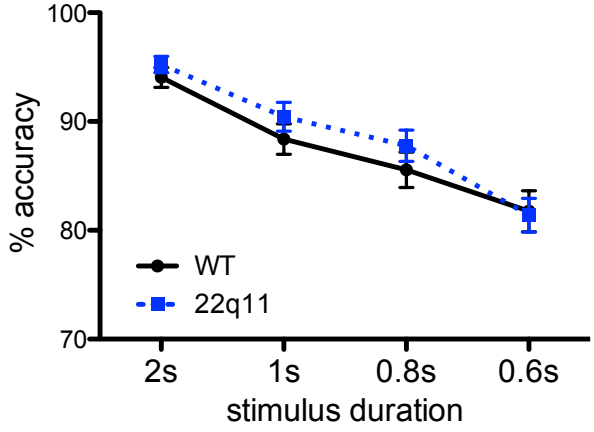


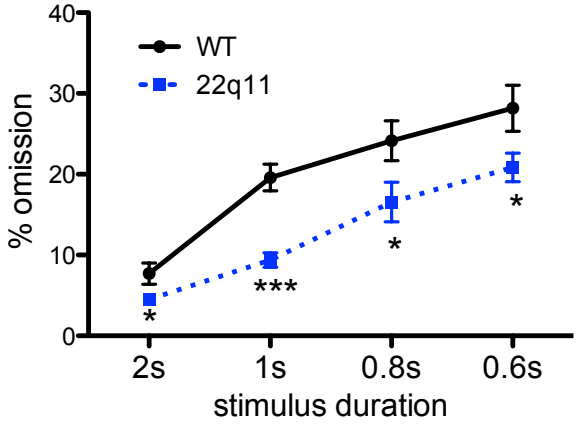


Increasing delays



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





Decreased omissions in TG after extended training

Mouse TUNL (UCAM)

Test of working memory

Sample phase

Delay

Baseline: 2s

Probes: 4s, 6s and 8s

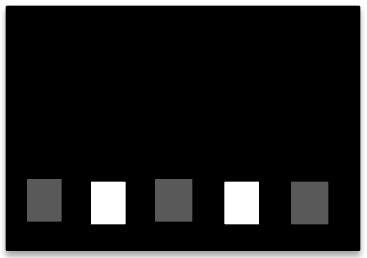
Test phase

Test of pattern separation

Sample phase

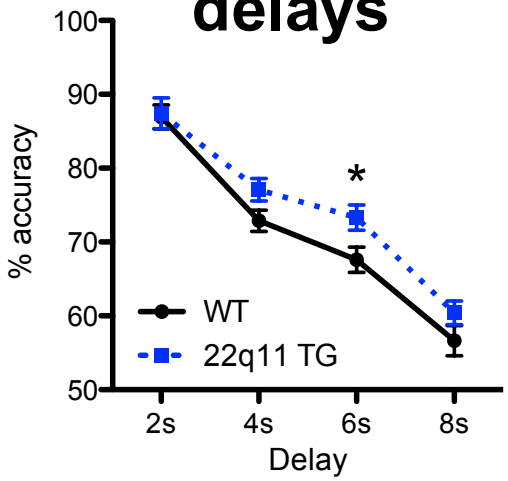
Delay (2s)

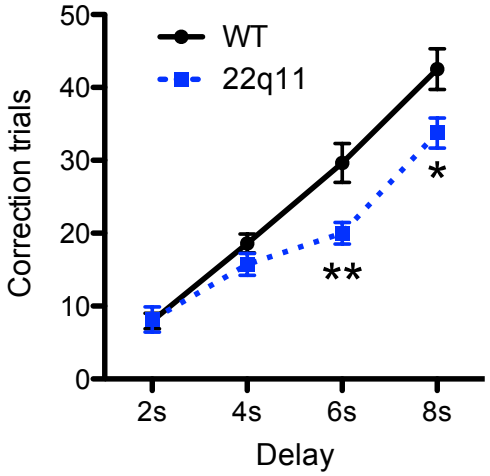
Test phase



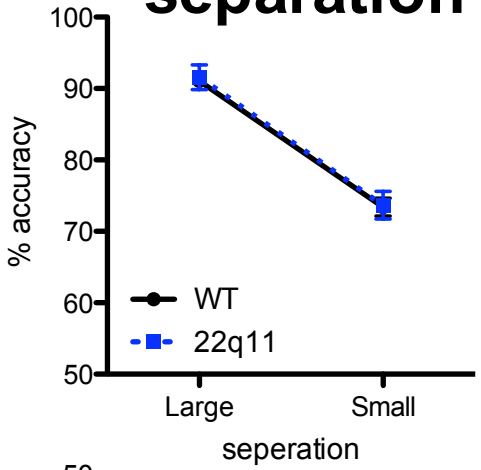
Mouse TUNL (UCAM)

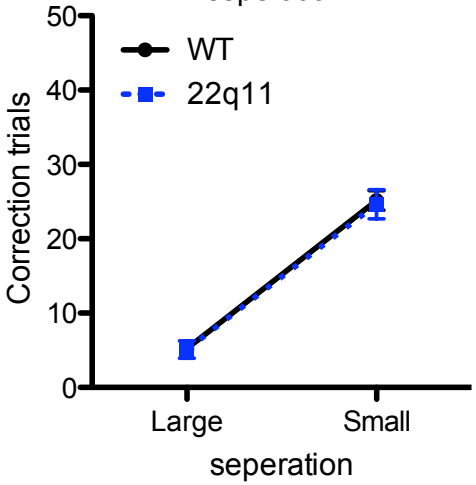
Manipulating delays





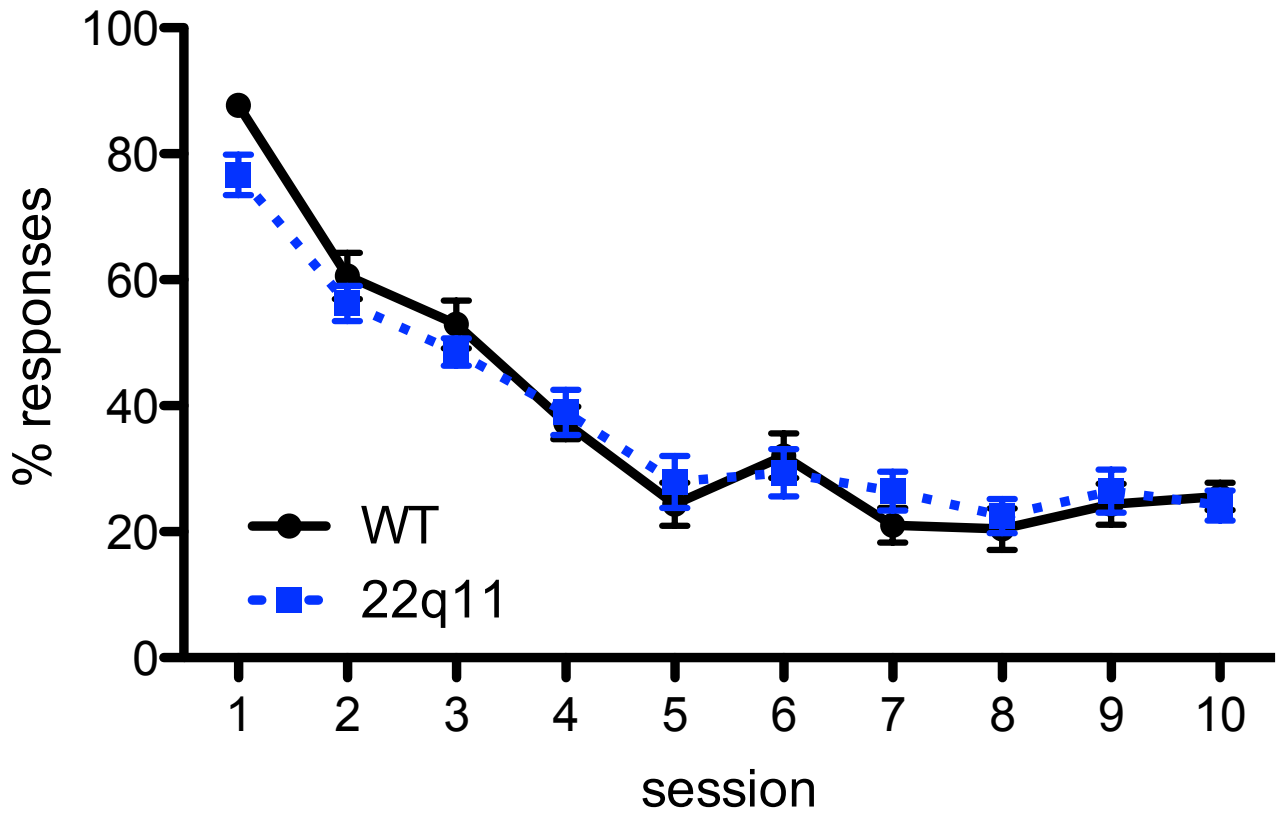
Manipulating separation





Sig. delay-dependent improvement in the TG on TUNL

Extinction learning (UCAM)



No significant effects of genotype on extinction

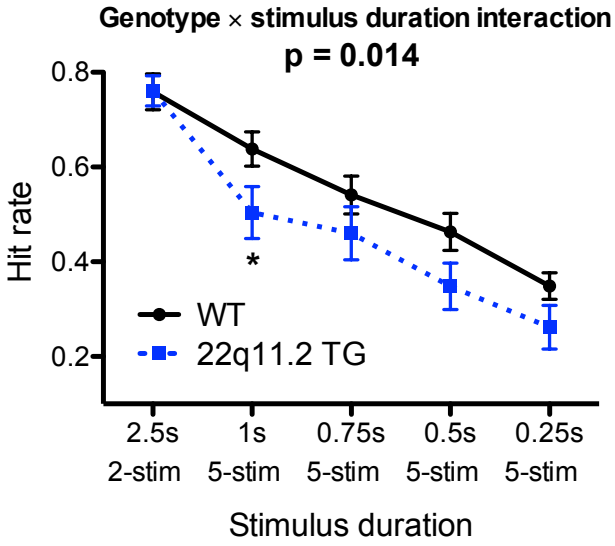
Genotype (p = .734)
Genotype x Session (p = .065)

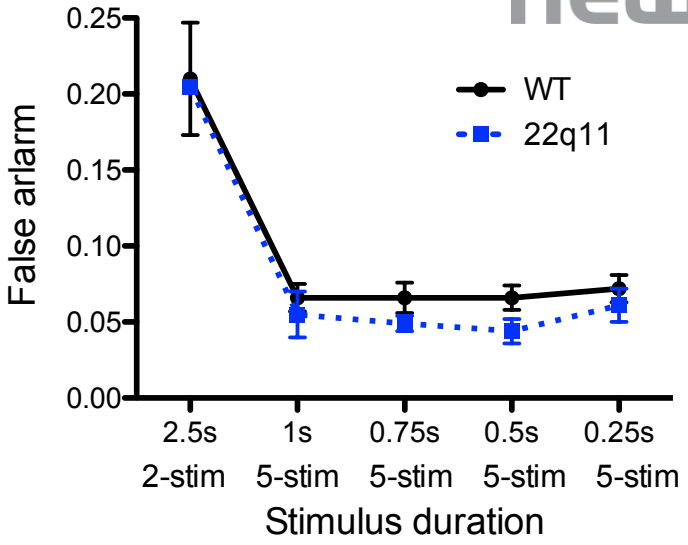
	UCAM	Lilly	Lundbeck	Mannheim
Watermaze	—	—	↔	—
NOR	↔	—	—	—
PVT	—	↔	—	—
FCON (Context + Cue)	—	—	↔	—
T-maze (Columbia)	(↓)	—	—	—
Automated T-maze	—	↔	—	—
Y-Maze	—	↔	↔	—
Touchscreen VD / REV	(↑)	—	—	—
Touchscreen PAL	↔	—	—	—
Touchscreen 5-CSRTT	(↑)	—	—	—
Touchscreen Extinction	↔	—	—	—
Bowl-digging ID/ED	—	—	—	Ongoing
Radial-arm maze	—	—	—	Ongoing
Social interaction	—	—	—	Ongoing
Touchscreen TUNL	↑	—	—	—

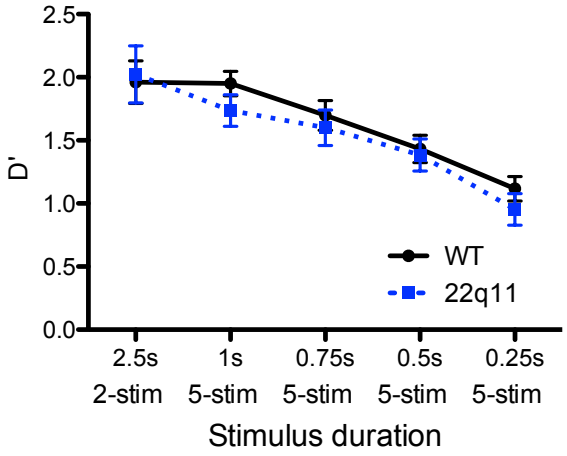
22q11 cognition manuscript - conclusions

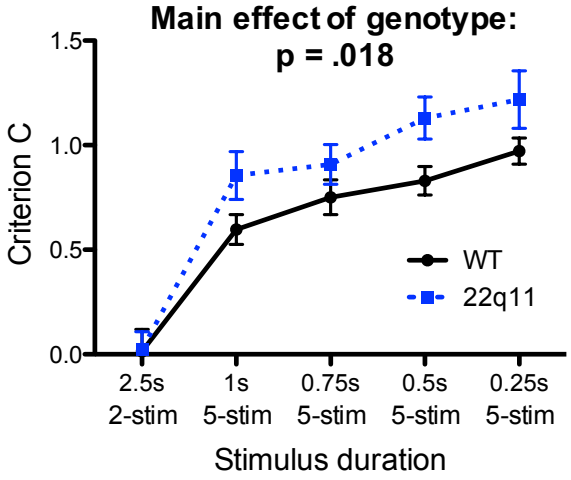
Although some trends towards impaired cognition, this extensive test-battery demonstrates that – overall – the 22q11.2 model shows few robust deficits exploitable for the use in drug-discovery within these tasks.

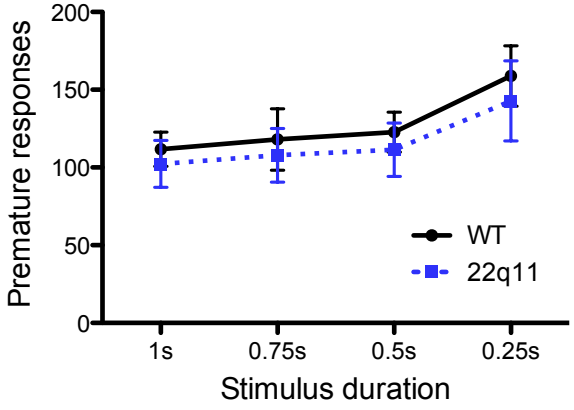
22q11 – Continuous Performance Task





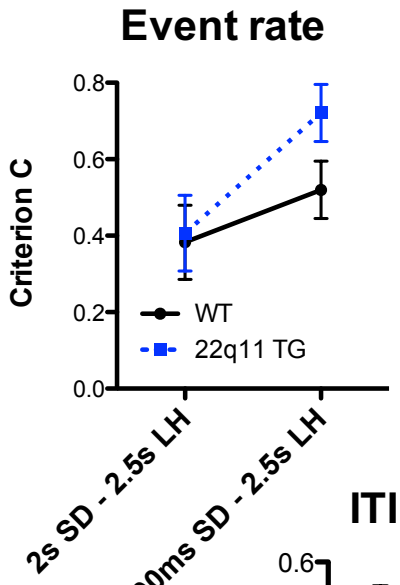


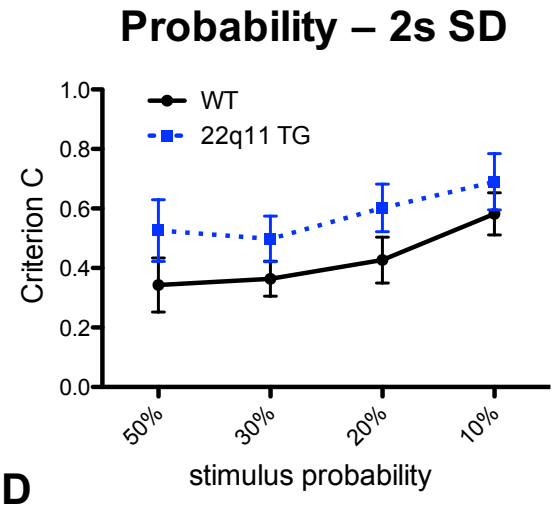


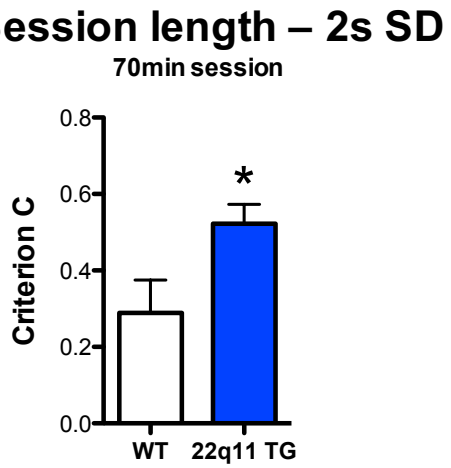


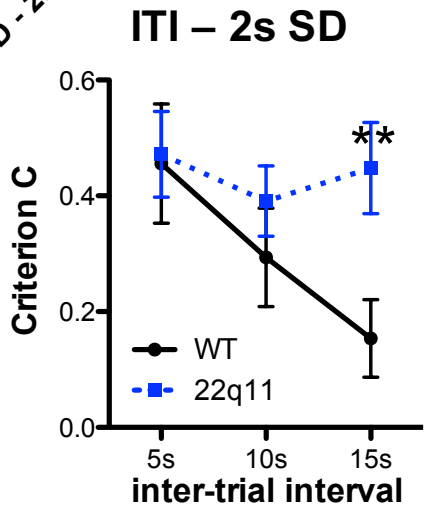
The transgenic respond less to both targets and non-targets

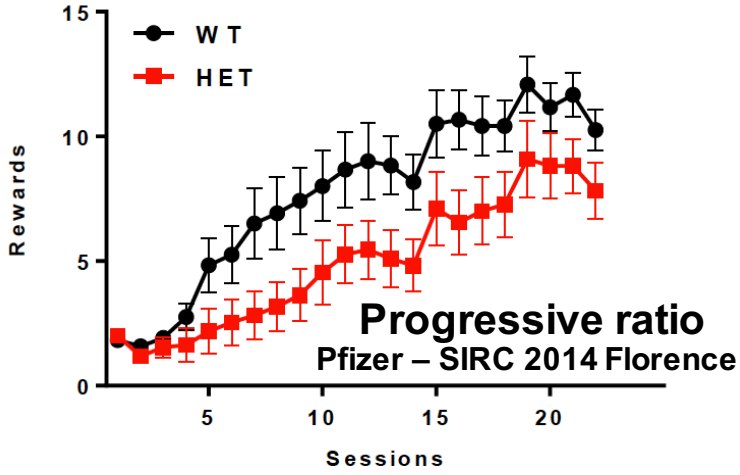
22q11 – Continuous Performance Task











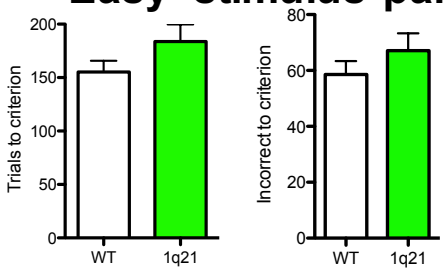
22q11 TGs respond less to targets and non-targets at long sessions and long ITIs. Experiment to be repeated. Currently tested on progressive ratio

Cognitive phenotyping of 1q21 TGs

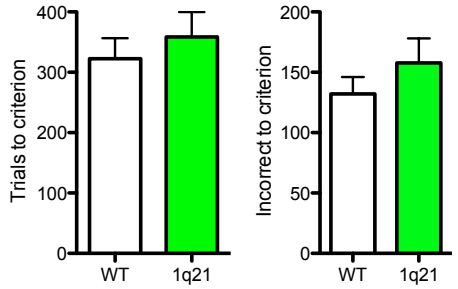
1q21: Impulsive phenotype in the 5-CSRTT

REVERSAL LEARNING

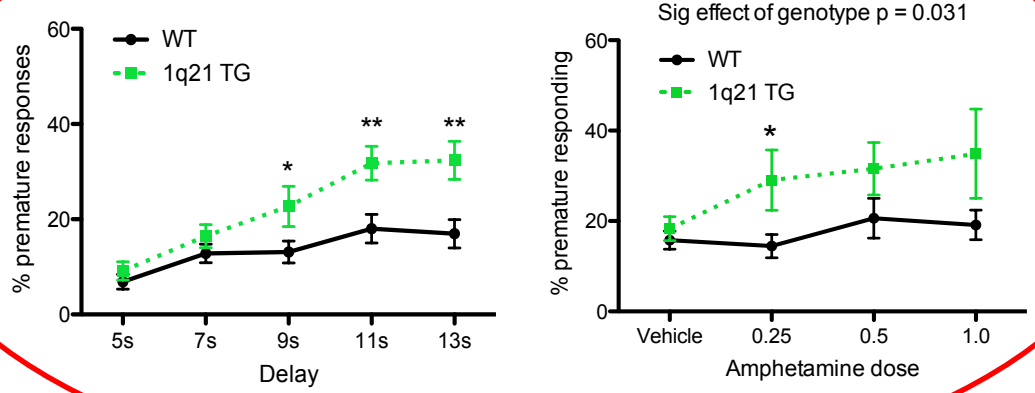
'Easy'-stimulus pair



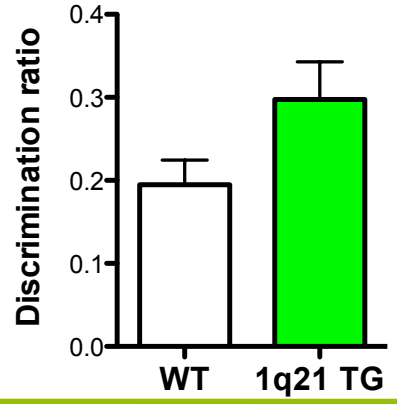
'Difficult'-stimulus pair



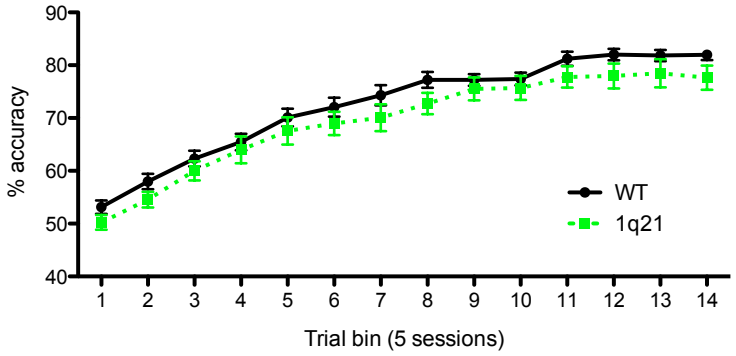
5-CSRTT



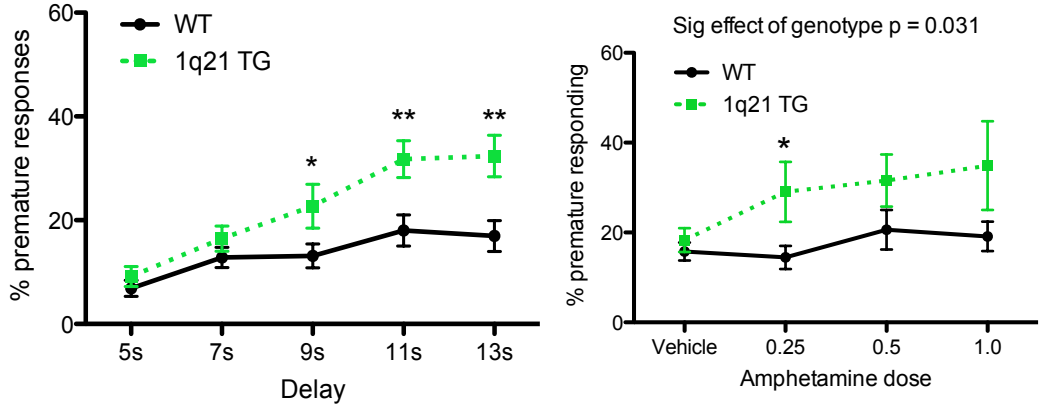
NOVEL OBJECT RECOGNISION



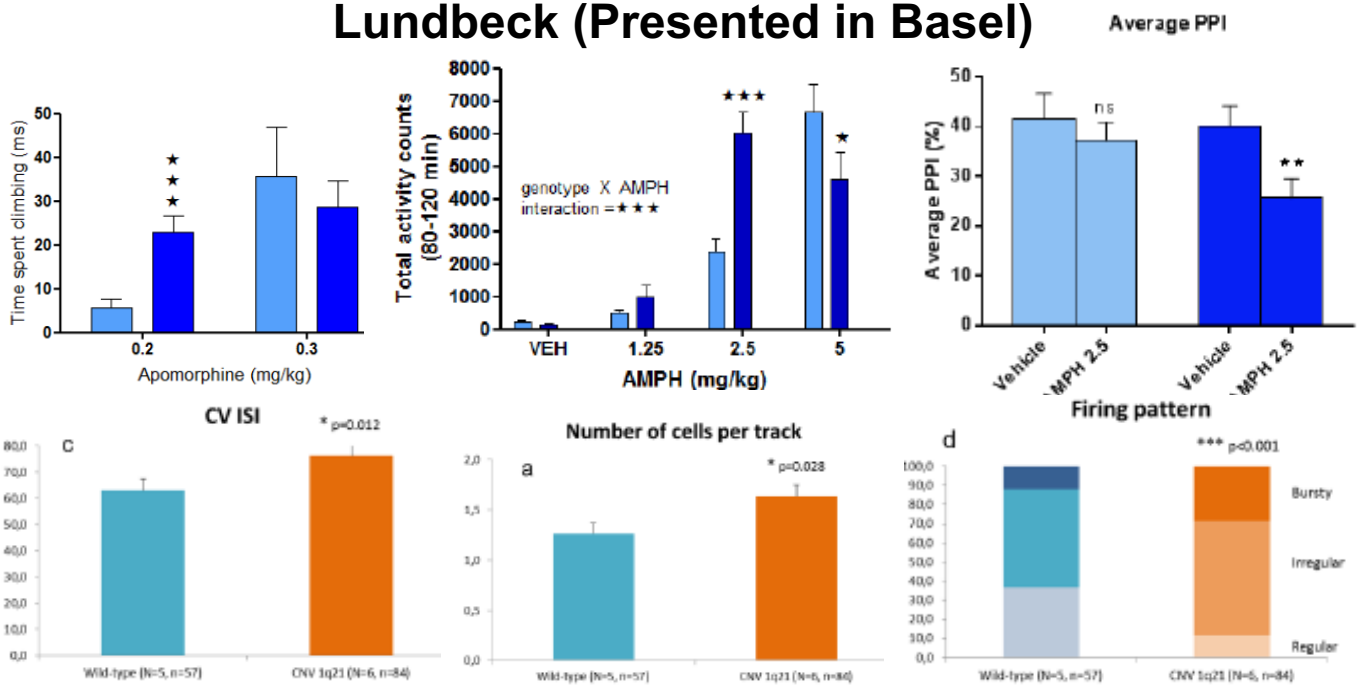
PAIRED ASSOCIATE LEARNING



Dopamine abnormality in the 1q21



Lundbeck (Presented in Basel)

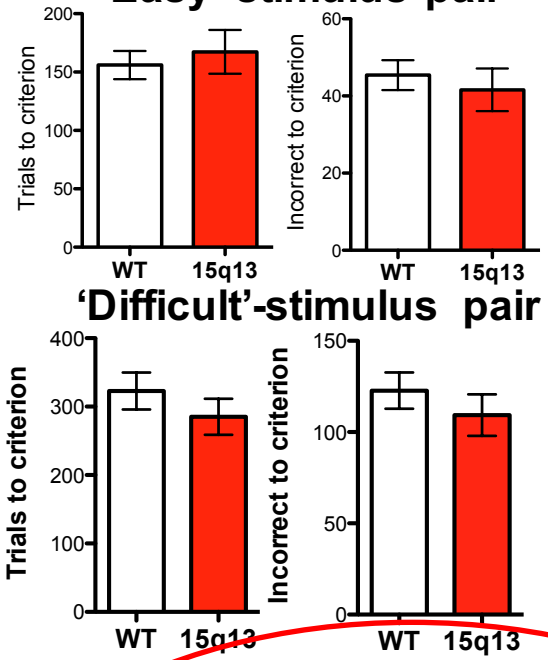


Currently tested on TUNL. CPT, and progressive ratio planned

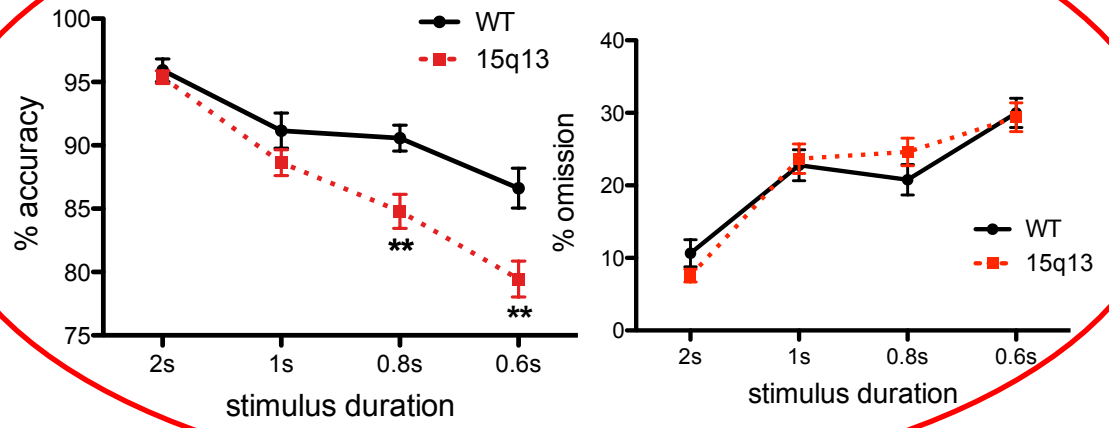
Cognitive phenotyping of 15q13 TGs

Impaired 5CSRTT and OR in 15q13 transgenic

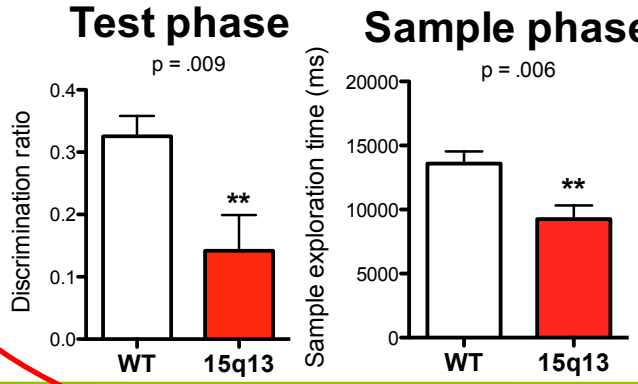
REVERSAL LEARNING



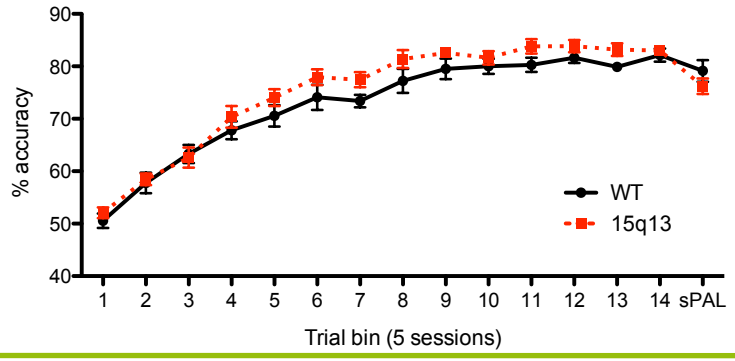
5-CSRTT



NOVEL OBJECT RECOGNISION



PAIRED ASSOCIATE LEARNING



SUMMARY

- No robust cognitive impairments in the 22q11.2 model on an extensive battery of touchscreen and traditional assays across sites
  - *Plan to replicate CPT-data and test on progressive ratio*
- No decisions regarding 1q21 and 15q13 dissemination
  - *Impulsive phenotype and DA-abnormalities in the 1q21 TG*
  - *Attentional and object recognition impairments in the 15q13 TG*
  - *Currently tested on TUNL, tests planned on CPT and progressive ratio*