The touchscreen 5-choice and mice carrying chromosomal microdeletions relevant to schizophrenia

Translational
Cognitive
Neuroscience

Simon Nilsson

Microdeletions of 22q11, 1q21, and 15q13

22q11

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

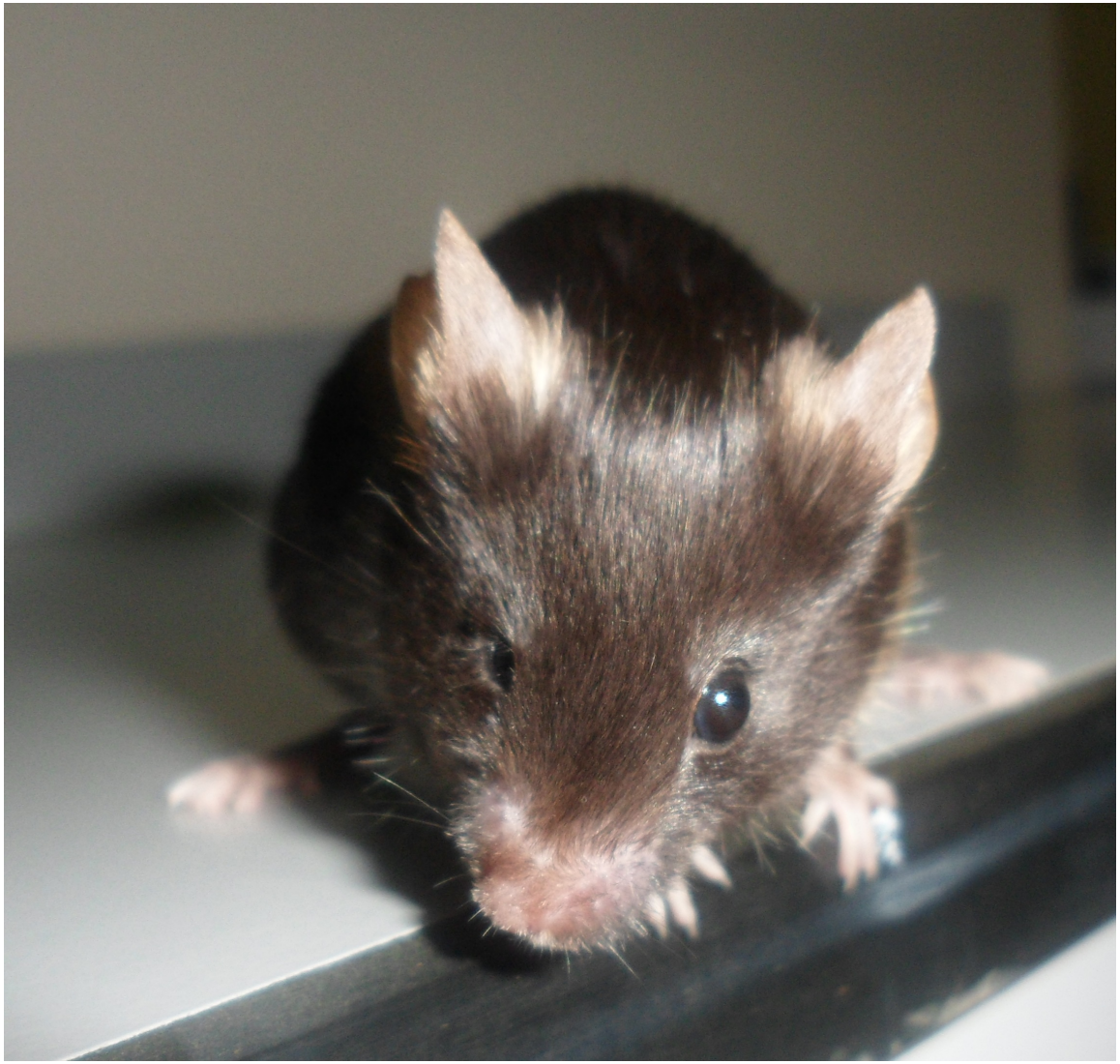
1q21

- PRKAB2
- FMD5
- CHD1L
- BCL9
- ACP6
- GJA5
- GJA8
- GPR89B

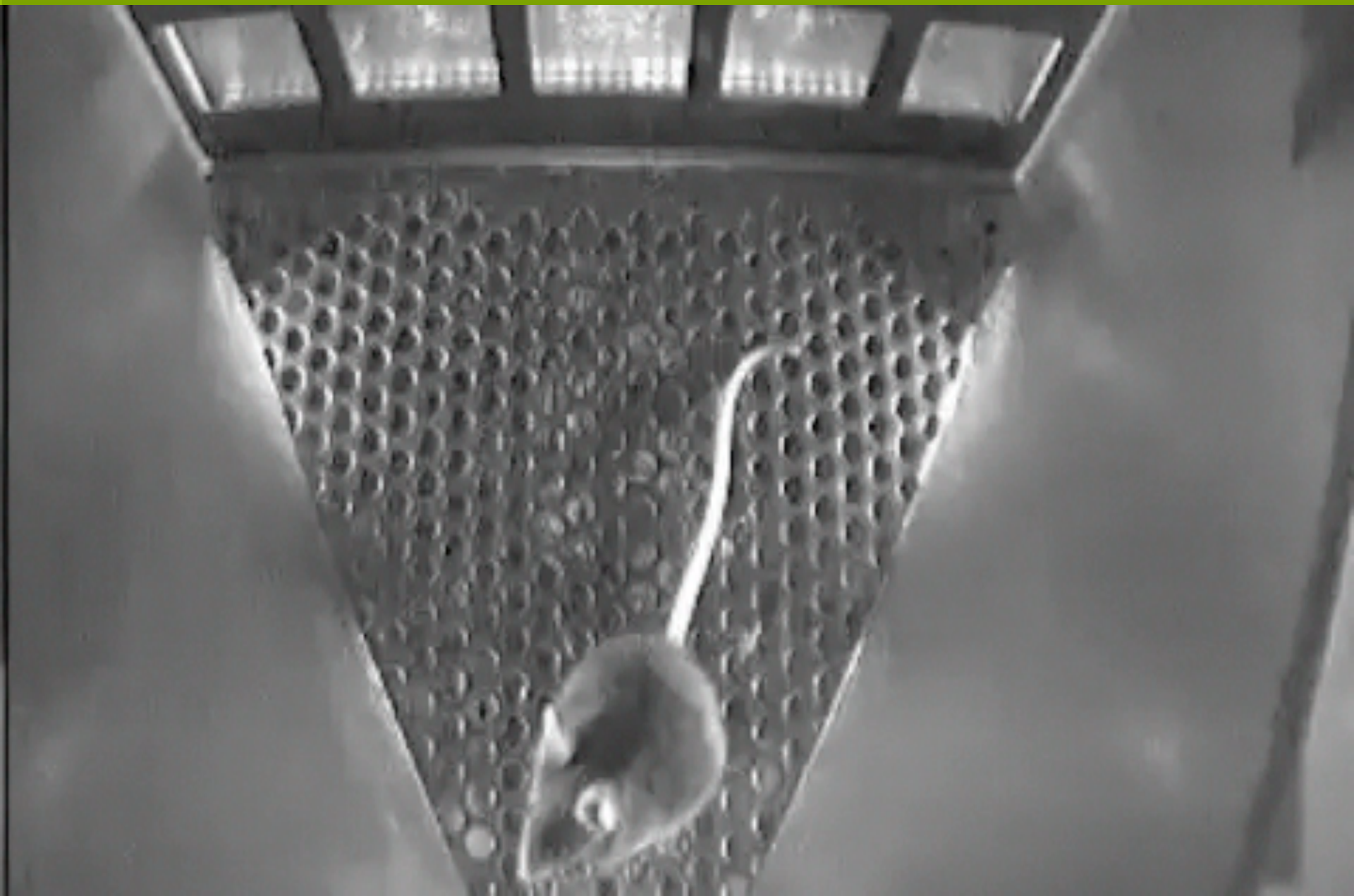
15q13

- CHRNA7
- OTUD7A
- KLF13
- TRPM1
- MTMR10
- MTMR15

Eye abnormality in the 22q11's



Touchscreen 5-choice



Touchscreen 5-choice method

- **22q11** (WTs = 16, TGs = 16)
- **1q21** (WTs = 16, TGs = 12)
- **15q13** (WTs = 16, TGs = 16)

Baseline:

2s SD, 5s delay, 40 trial session length.
≥ 80 % accuracy and ≤ 20 % omission x 2 consecutive sessions
(Romberg et al. *J Neurosci* 2012)

Probed on:

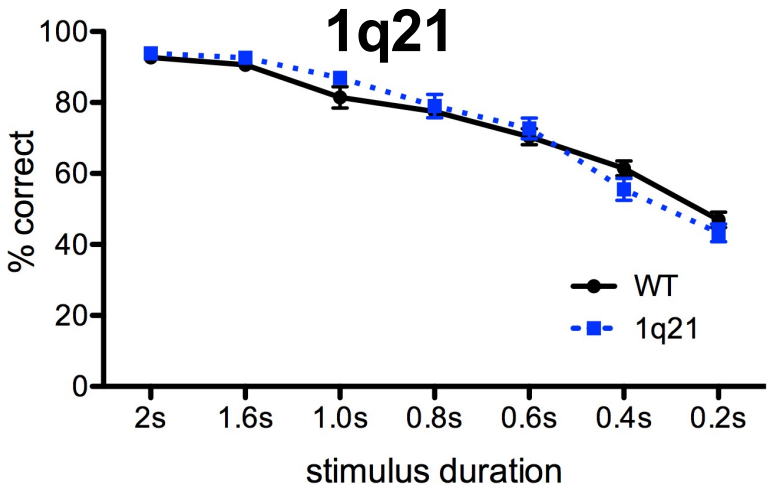
Shorter stimulus durations (1.6, 1s, 0.8s, 0.6s, 0.4s, 0.2s) – **no effect of genotype**

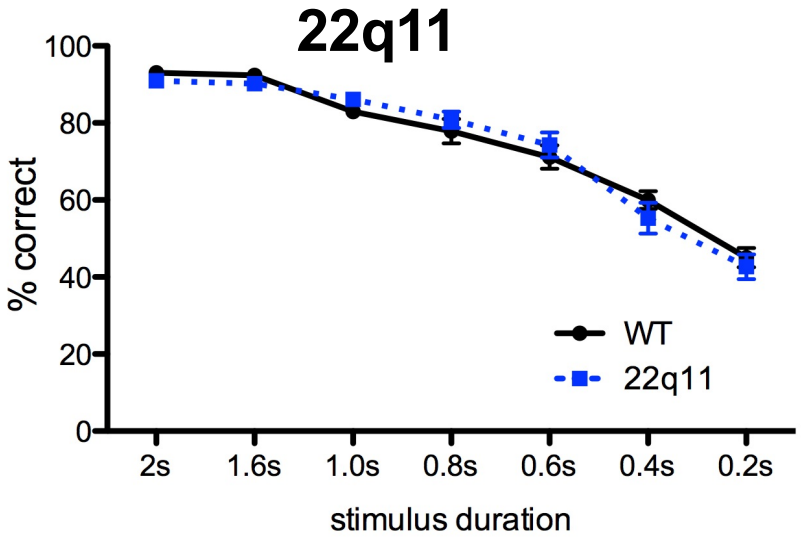
Longer delays (7s, 9s, 11s, 13s)

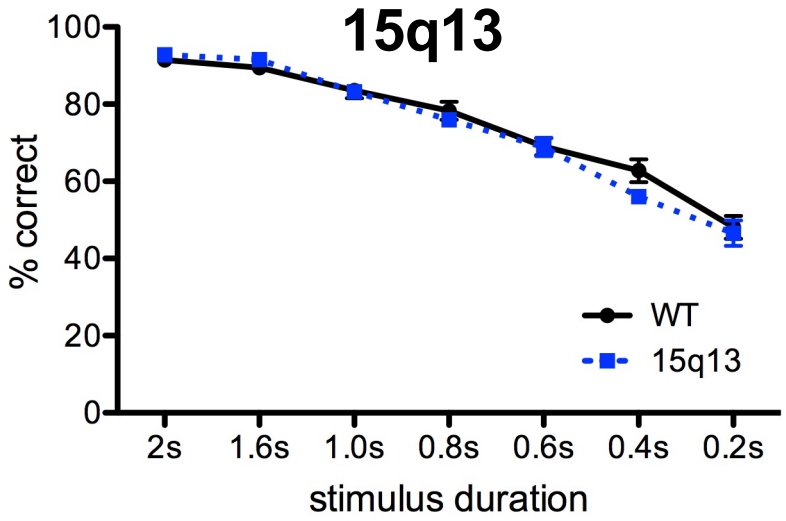
Longer sessions and decreased SDs (80 trials, 140 trials – 1s, 0.8s, 0.6s)

Each probe lasts for two consecutive days, with 1 baseline session between each probe (≥ 80 % accuracy, ≤ 20 % omission)

Accuracy – decreasing stimulus durations

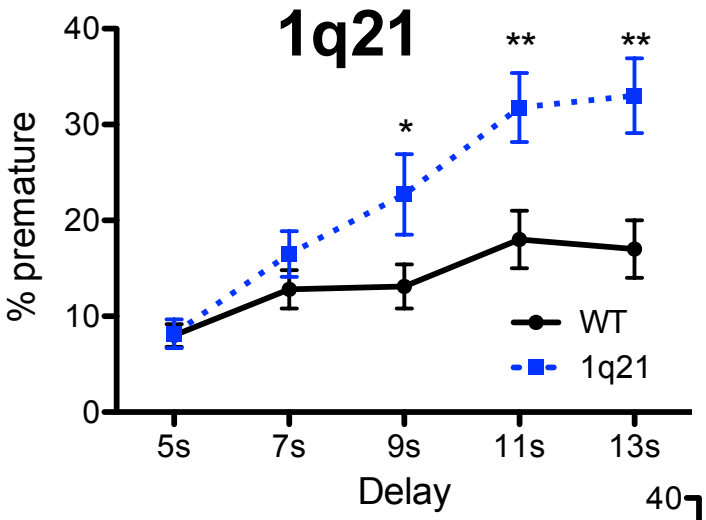


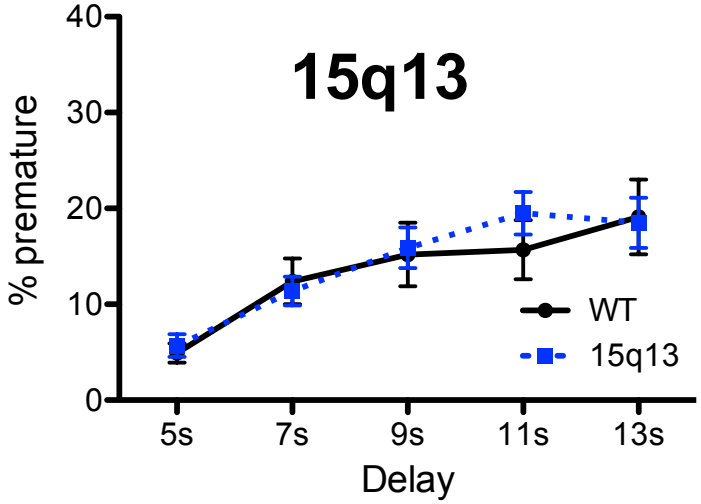


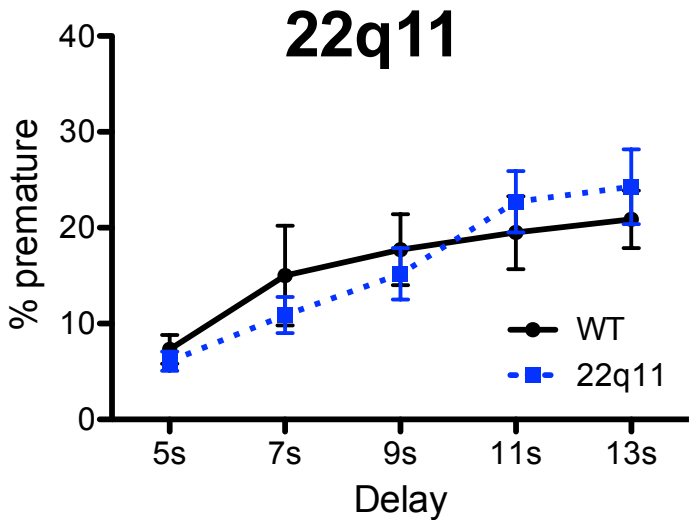


No effect of genotype

Longer delays







Increased premature responding in 1q21's at longer delays
No effect of genotype in the 15q13 and 22q11's experiments

Premature responding in the 1q21's

- Increased dialysis DA in DStr/NAc in response to amphetamine
- Elevated hyperactivity in response to amphetamine (but not the D1 agonist SKF81297)
- Decreased PPI in response to PCP and amphetamine.

Dose with D2-antagonist sulpiride

Sulpiride in 1q21's

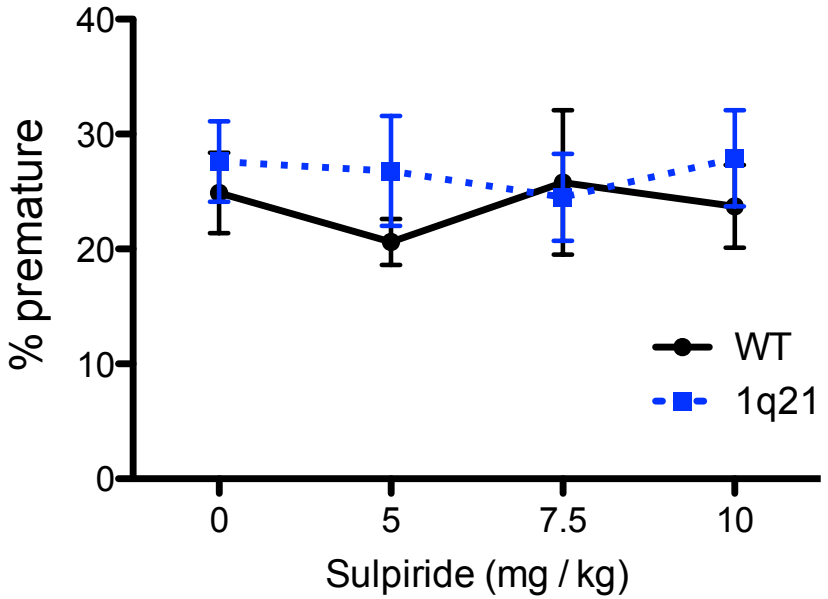
-(-) Sulpiride 0, 5, 7.5, 10 mg/kg - latin-square

20min pretreatment, i.p.

Dosed at 13s delay

Each dose separated by 4-day washout at 5s delay

Sulpiride in 1q21's at 13s delay

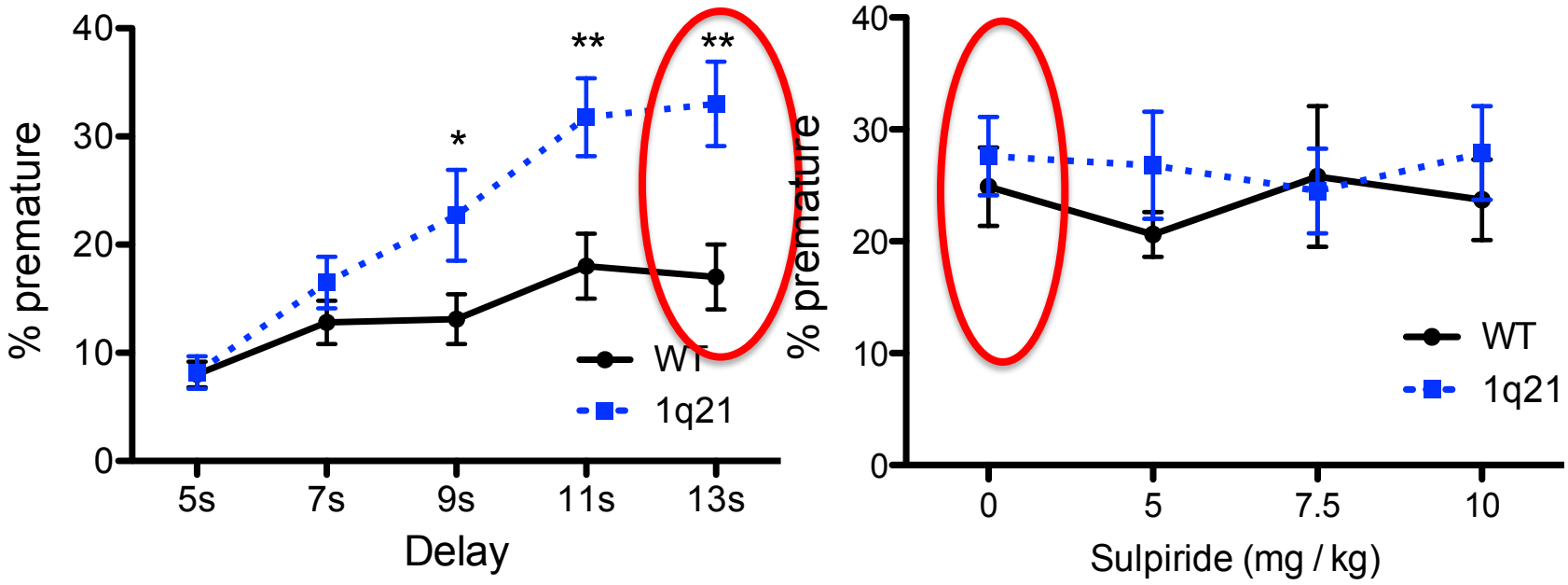


No longer a genotype difference in premature responding

No effect of sulpiride on premature responding

Genotype differences masked by injection-stress in WT's and adaptation in TG's (?)

Sulpiride in 1q21's at 13s delay



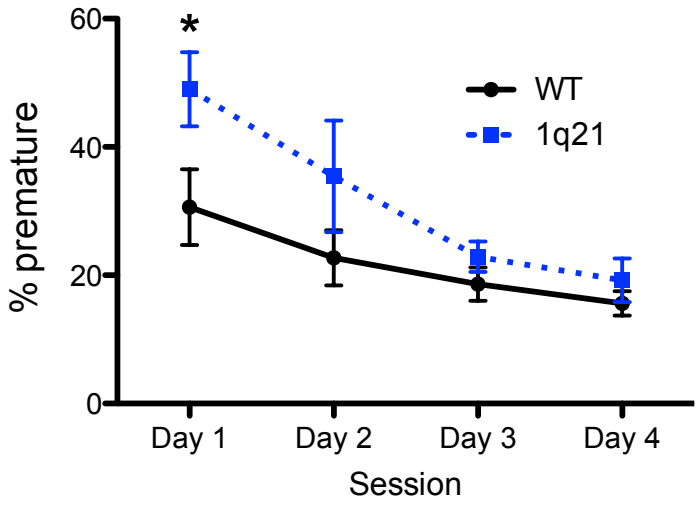
Genotype differences possibly masked by (?):

Injection-stress in WT's,

Adaptation in TG's

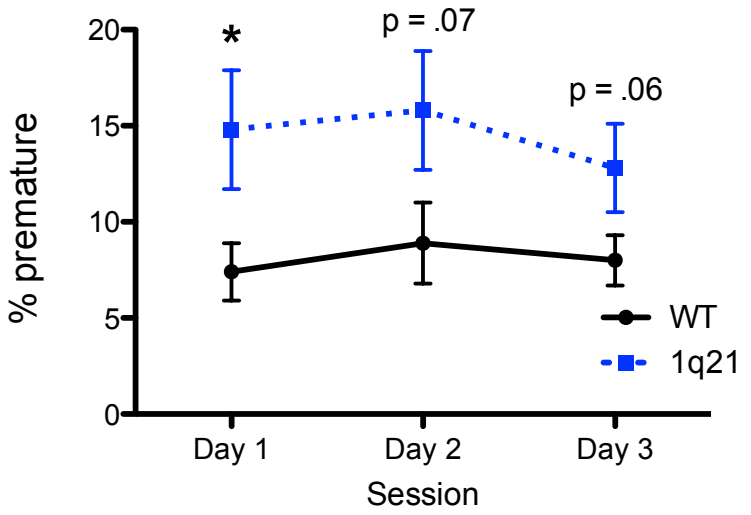
Further testing with long delays

14 days rest → 9 days on 5s delay→ 4 days on 13s delay



Adaptive responding in 1q21's

3 days on variable delays
80 trial sessions
5s (60% of trials) 13s (40% of trials)



Low number of premature responses and large errors in TG group.

Relatively stable increase in 1q21's

Sustained attention in 15q13 and 22q11's

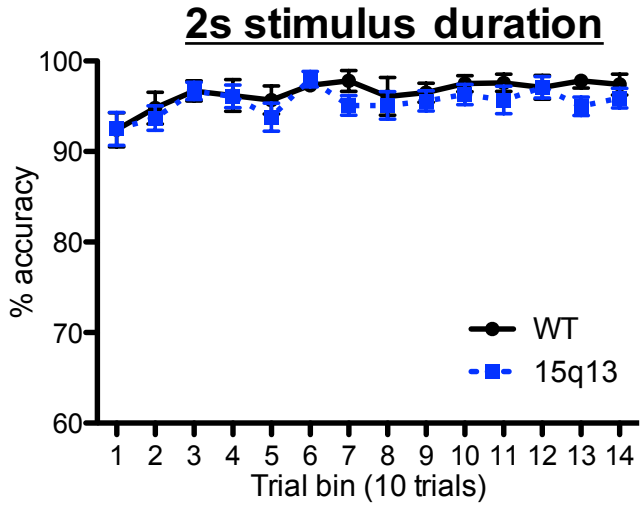
80 trials session – 2s SD baseline

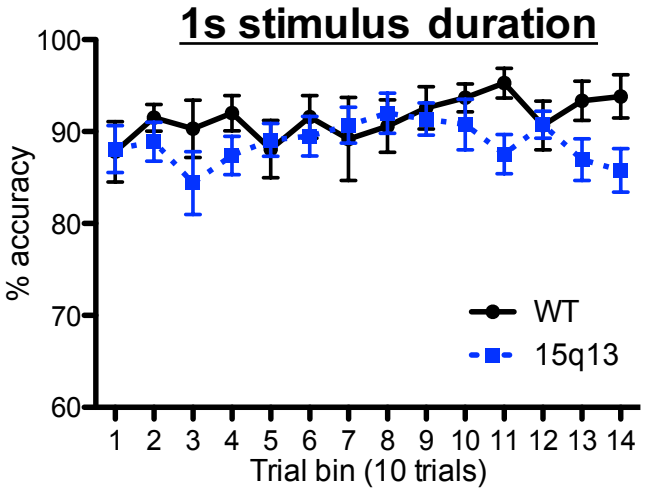
Probed on 1s, 0.8s SDs

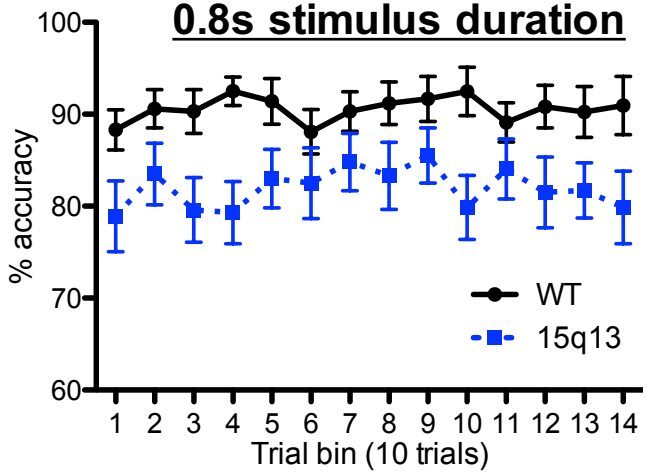
140 trials session – 2s SD baseline

Probed on 1s, 0.8s, 0.6s SDs

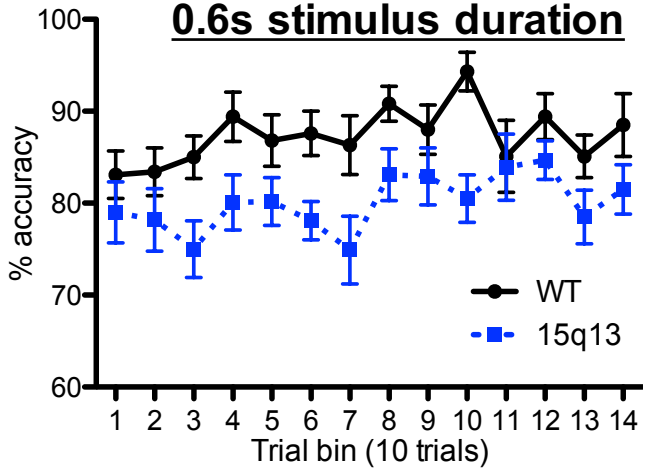
15q13 - Accuracies over **140 trials**







Sig. effect of genotype p < 0.01



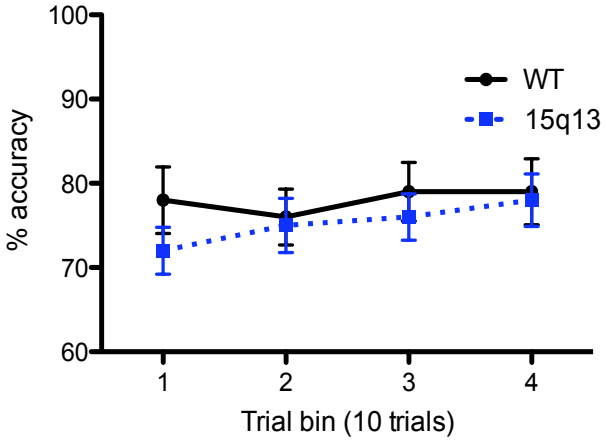
Sig. effect of genotype p = 0.001

No effect of trial-bin on accuracy. Sig. effect of genotype at shorter SD's

Accuracy 0.8s SD at 40, 80, and 140 trials

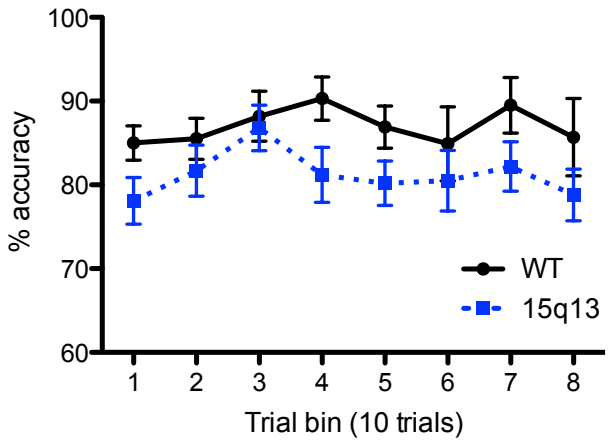
15q13

40 trials



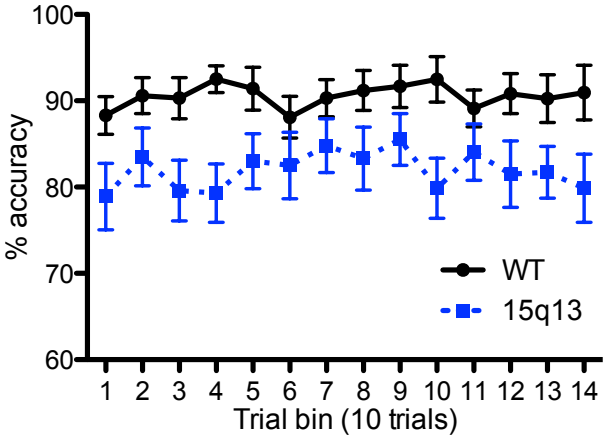
Test day ≈ 54
Animal age: 19 weeks

80 trials



Test day ≈ 92
Animal age: 25 weeks

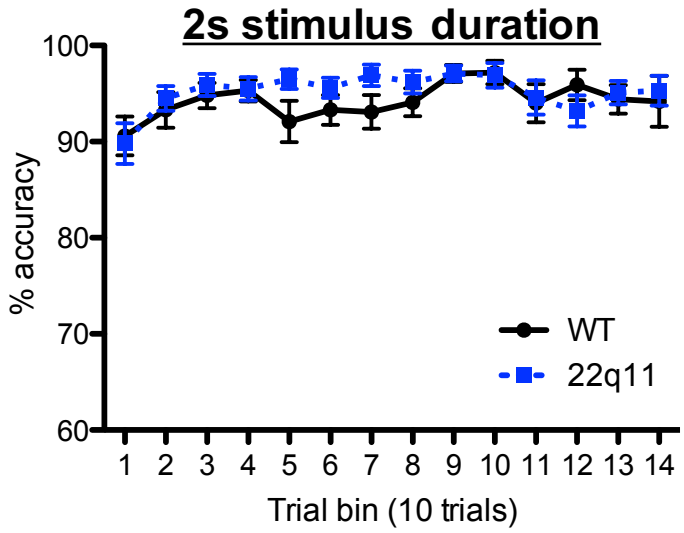
140 trials

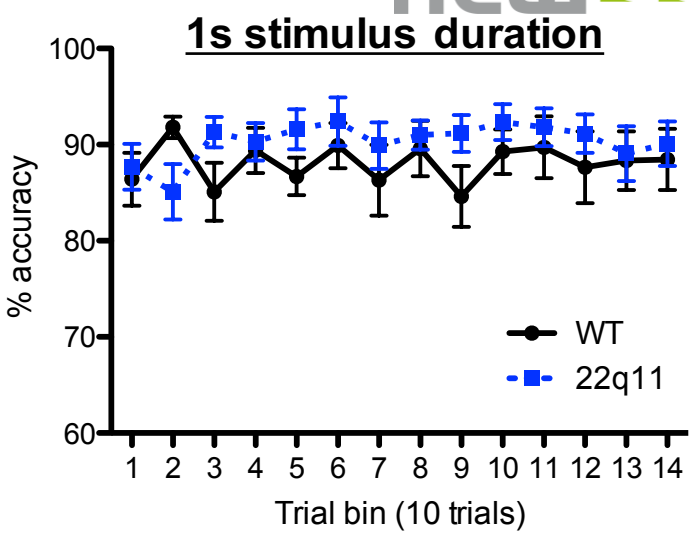


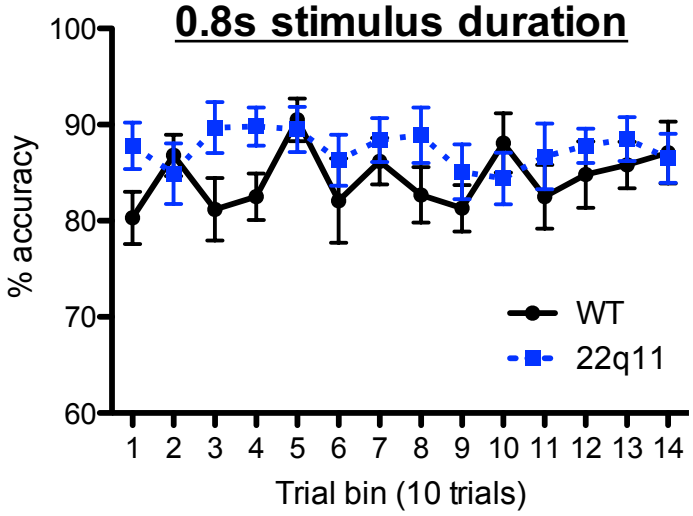
Test day ≈ 105
Animal age: 27 weeks

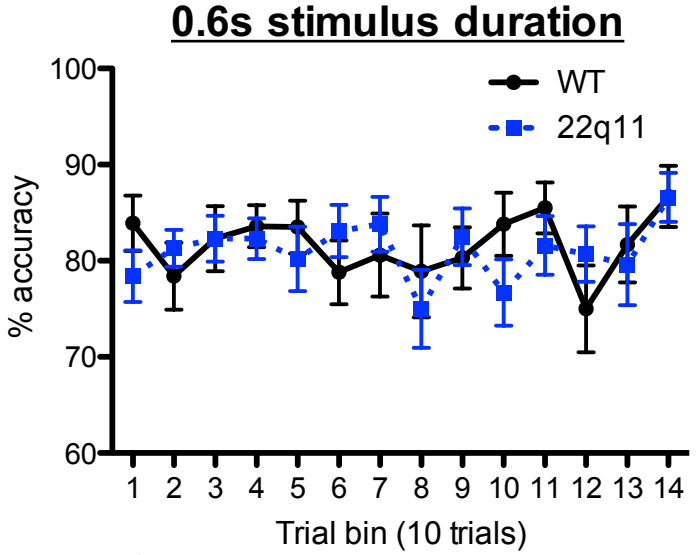
Prolonged training unmasks accuracy impairment in 15q13 TG's

22q11 Accuracy over **140 trials**



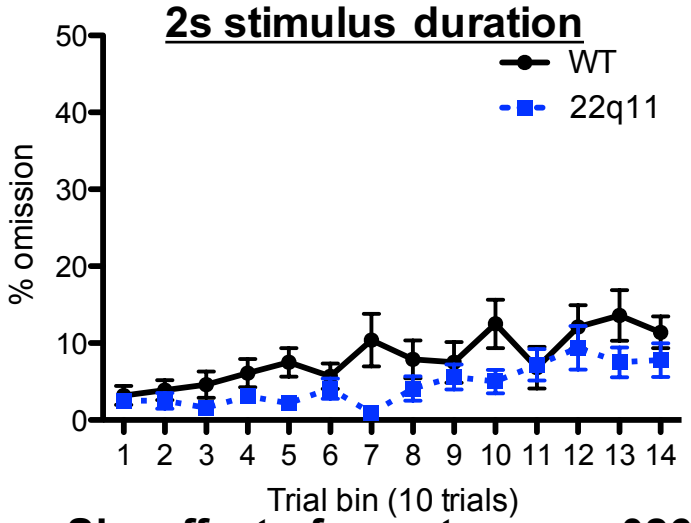




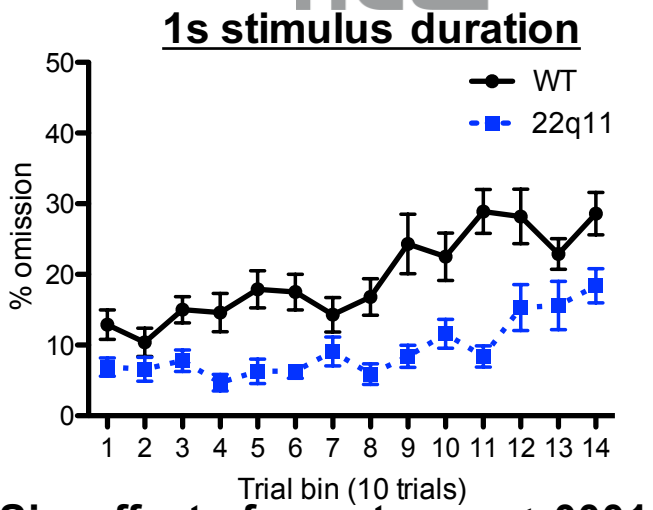


No effect of genotype

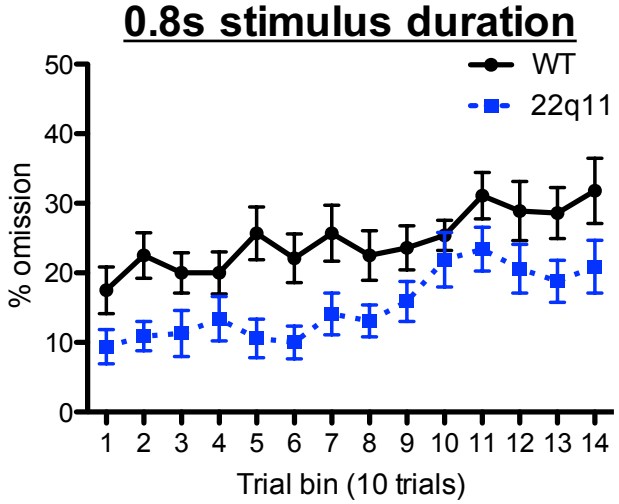
22q11 - Omissions over **140 trials**



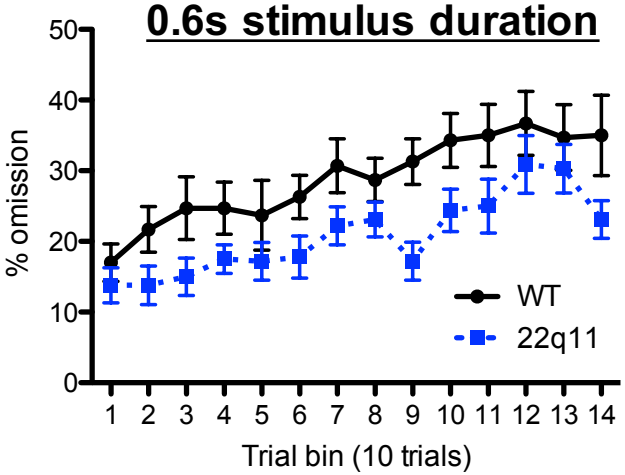
Sig. effect of genotype p = .026



Sig. effect of genotype p < .0001



Sig. effect of genotype p = .031



Sig. effect of genotype p = .021

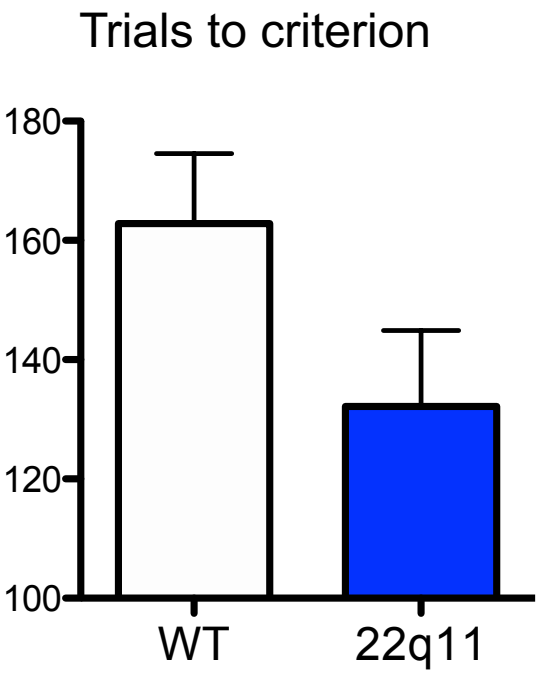
Sig. effect of genotype at all stimulus durations

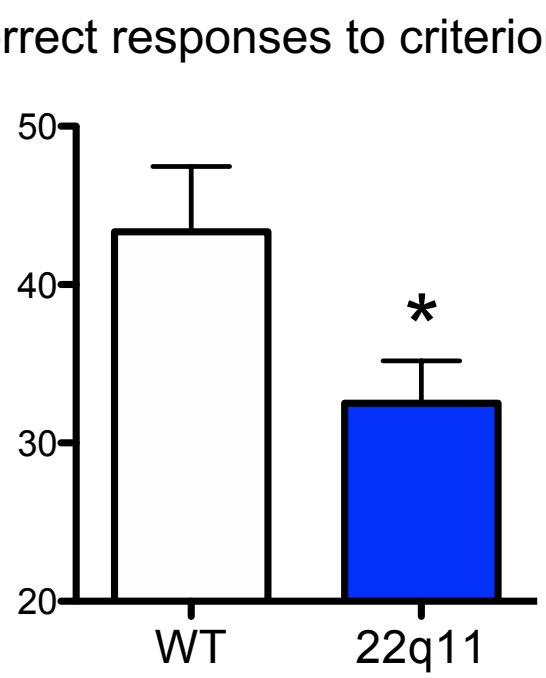
Summary and what's next

- **1q21** — **Increased premature responding at longer delays**
  Currently exploring suitable protocols for pharmacology
- **15q13** — **Decreased accuracy with prolonged training**
  Effect replicated and considering pharmacology
- **22q11** — **Decreased omissions with prolonged training**

- **Visual reversal learning**
  In new batches of each genotype
- **Exploit novel mouse tests**

Improved visual discrimination in 22q11's

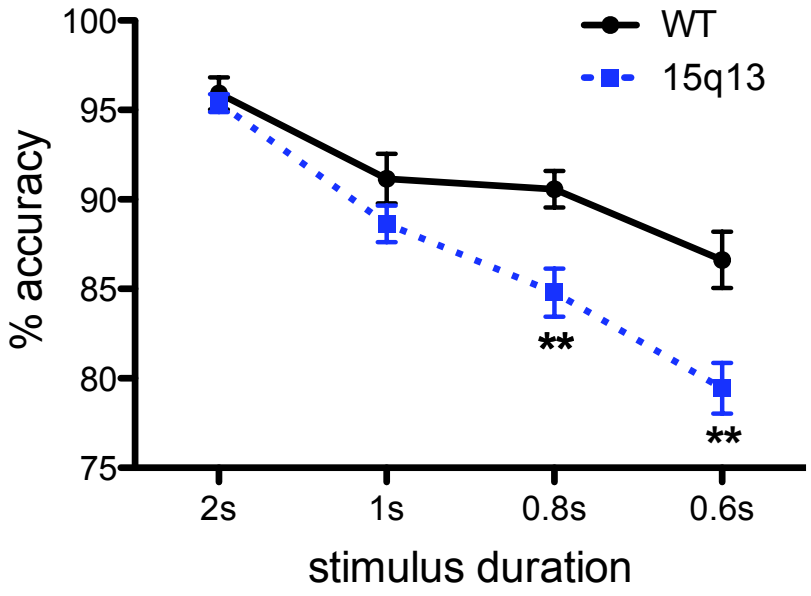




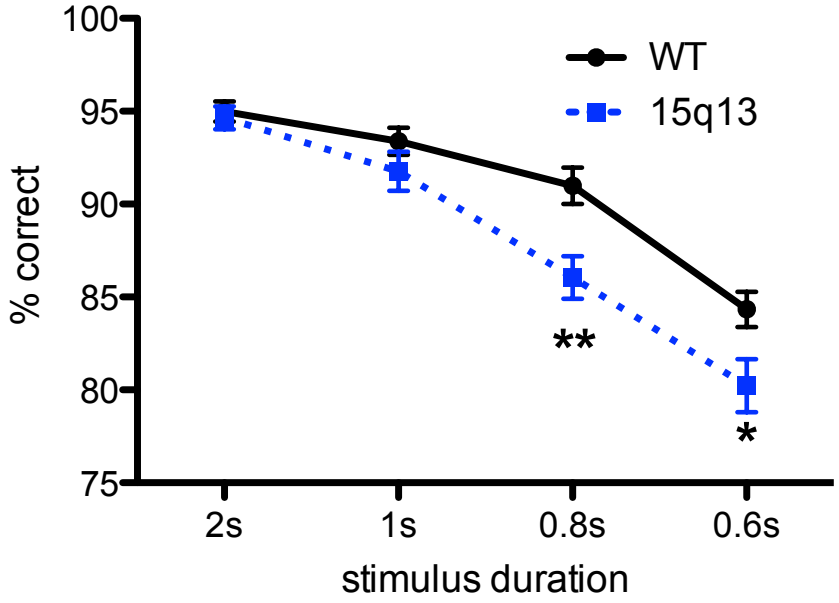
Criterion: ≥ 80% accuracy × 2 consecutive sessions

Replication of 15q13 accuracy deficit

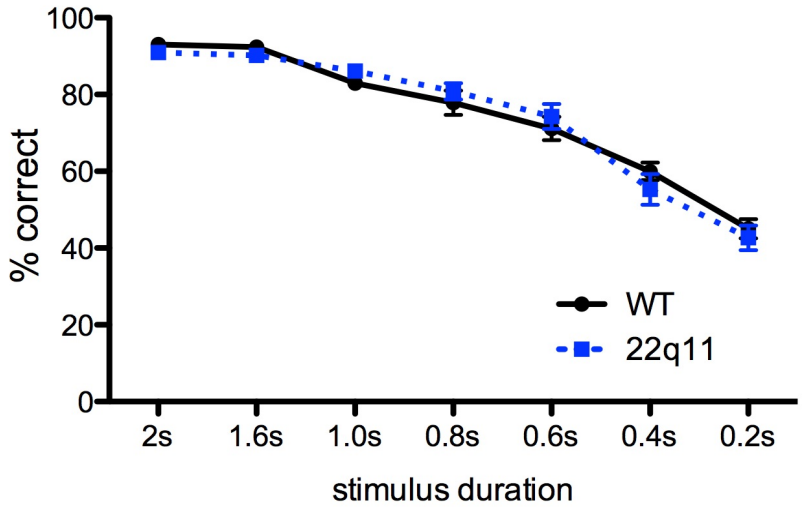
Dec 2012

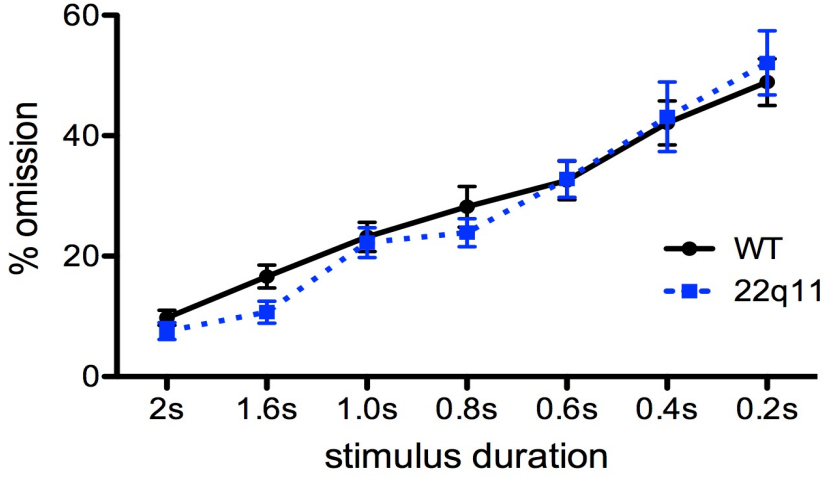


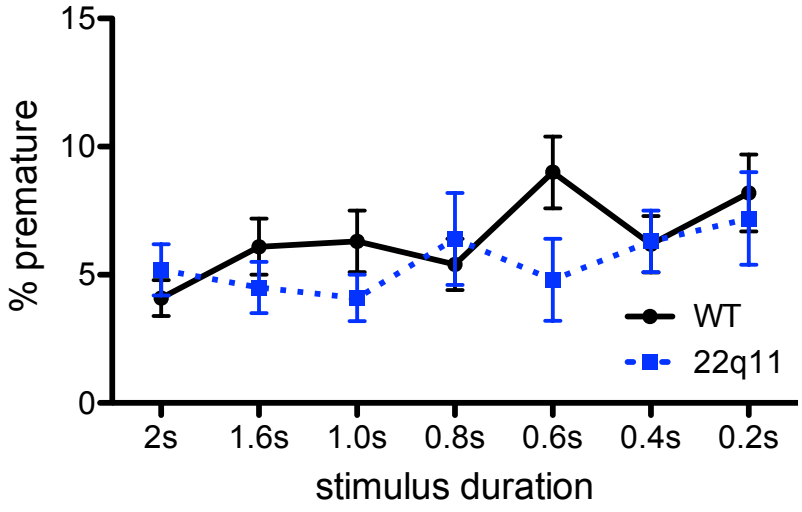
Feb 2013

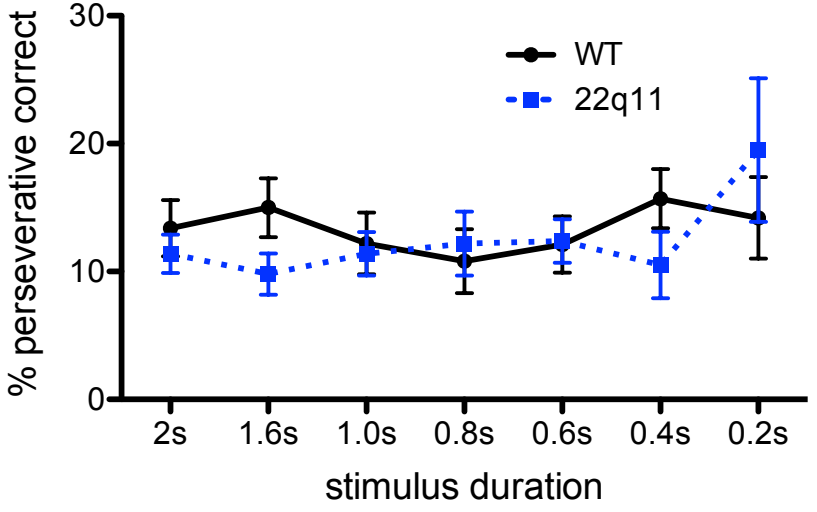


22q11 – decreasing stimulus duration
(Test day: 37-68, Animal age: 17 – 22 weeks)



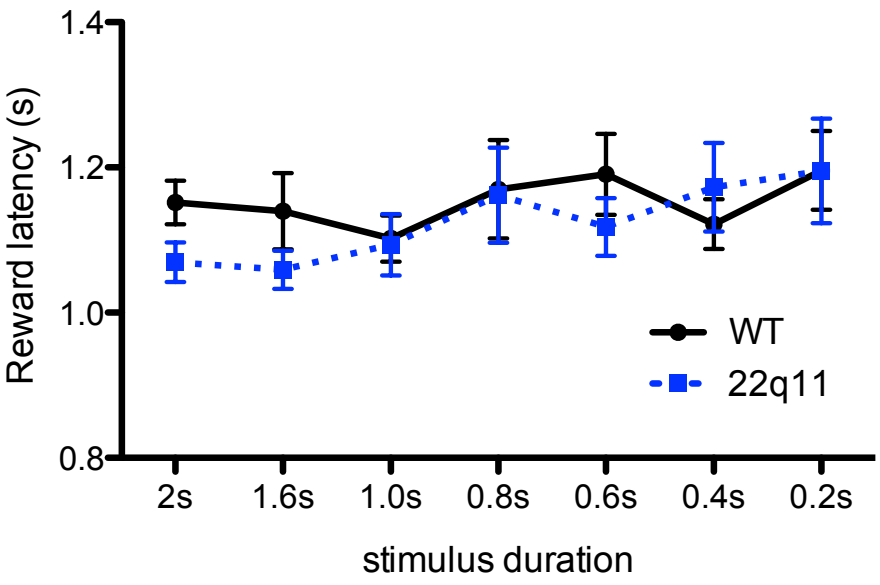


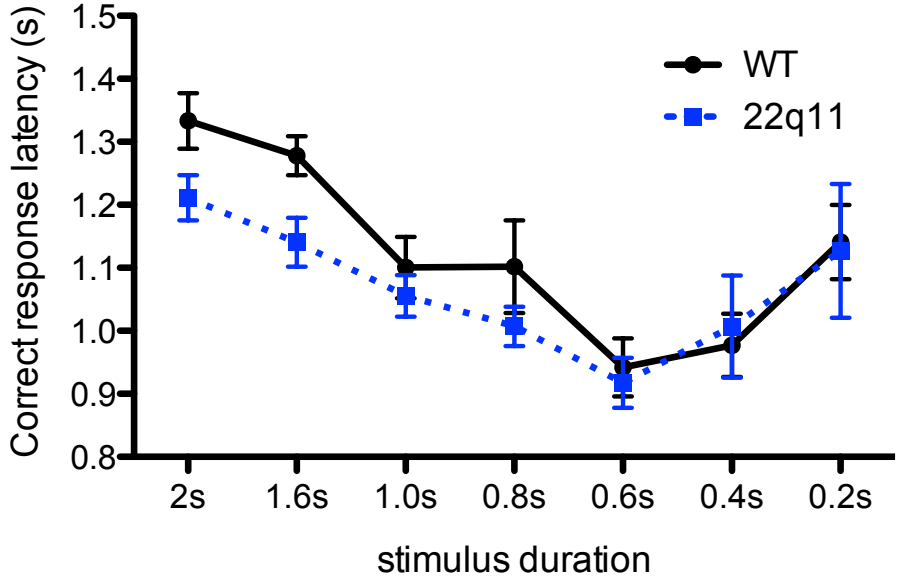




No effect of genotype

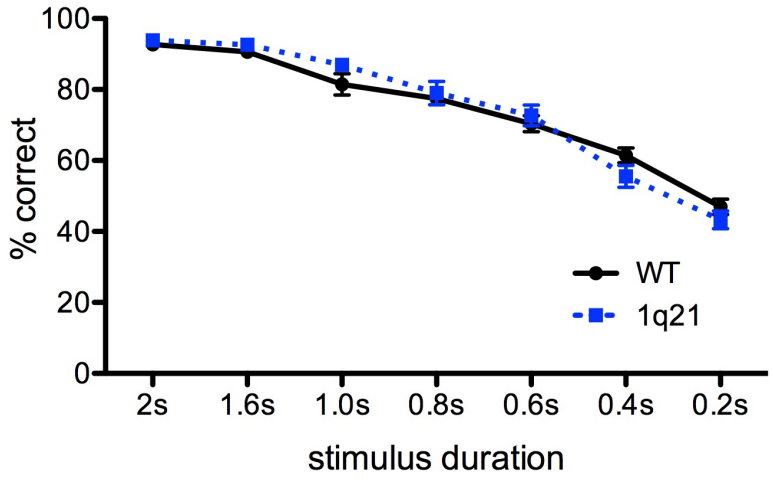
22q11 – decreasing stimulus duration

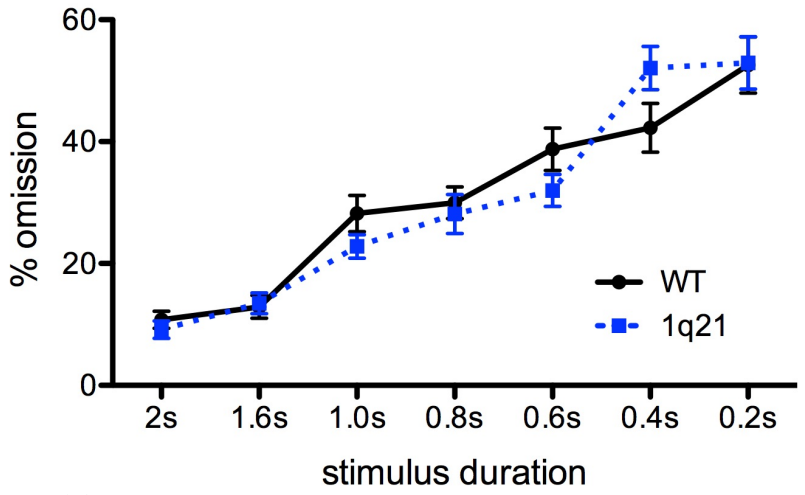


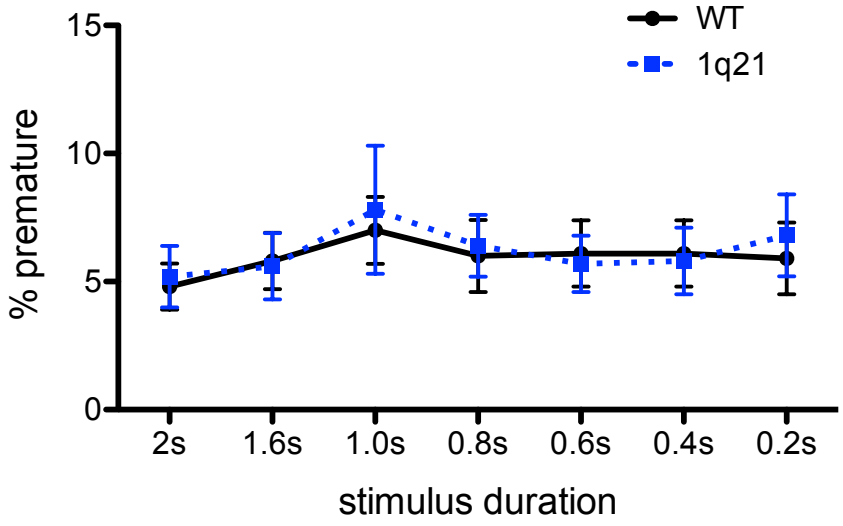


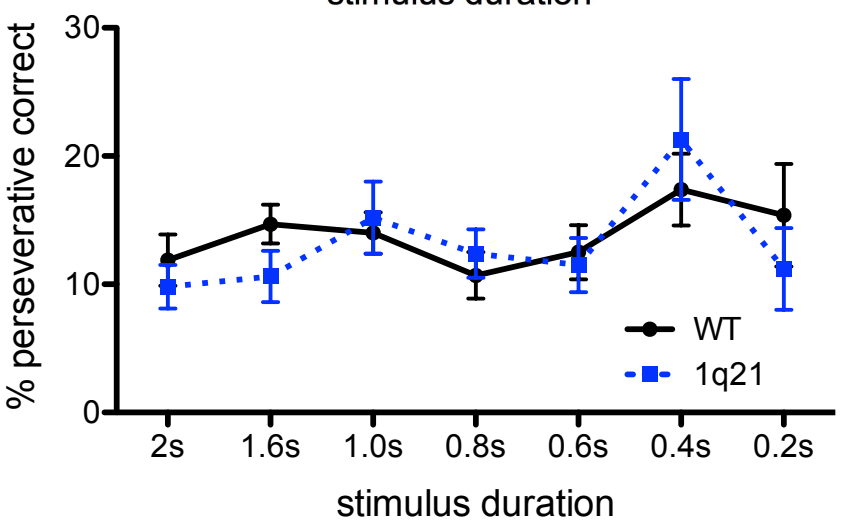
No effect of genotype

1q21 – decreasing stimulus duration
(Test day: 37-68, Animal age: 17 – 22 weeks)



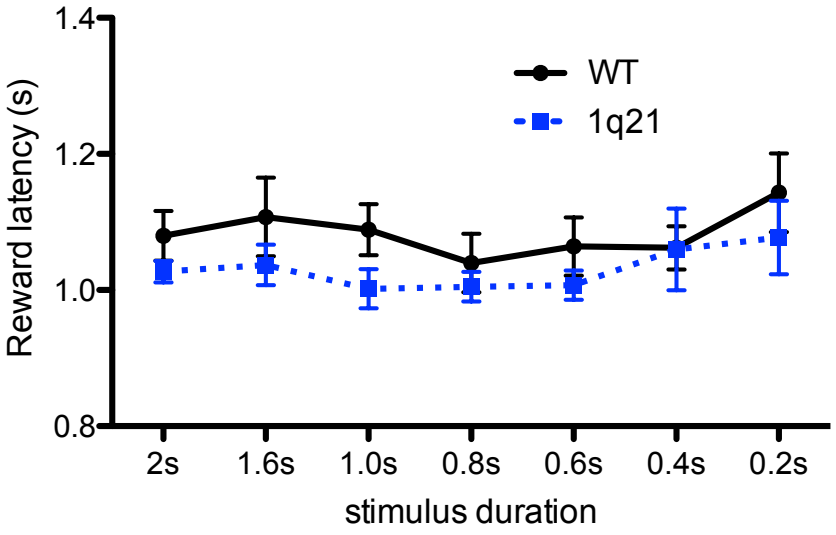


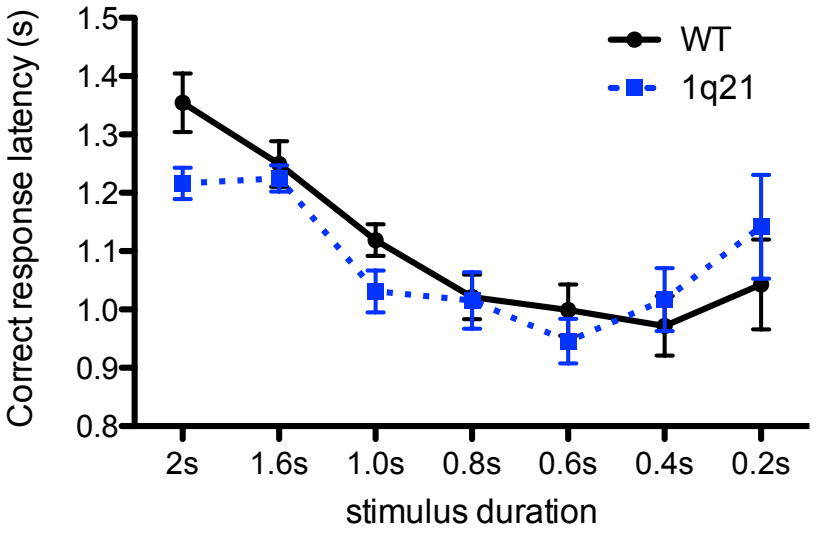




No effect of genotype

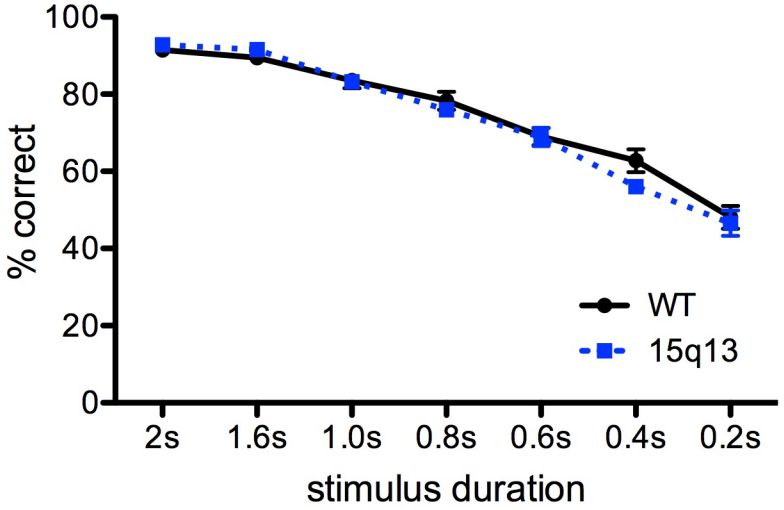
1q21 – decreasing stimulus duration

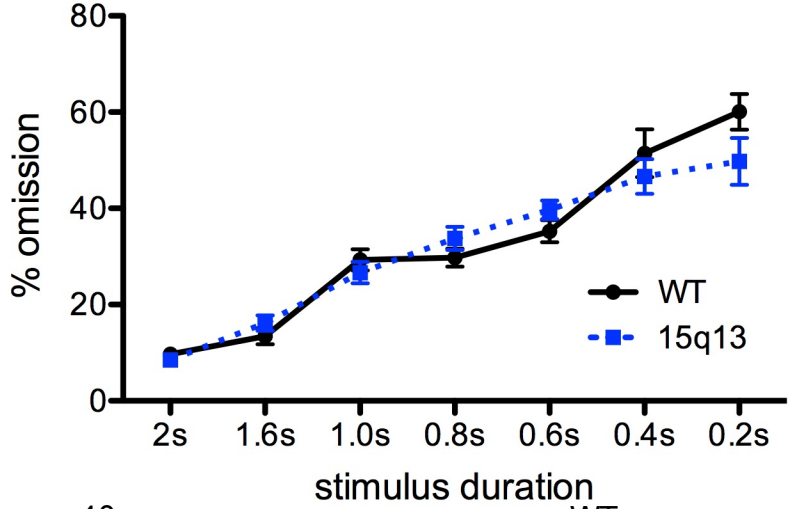


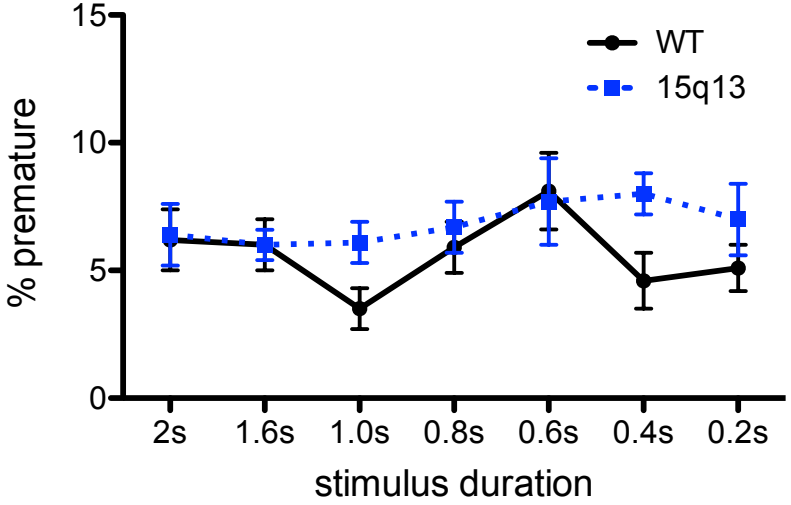


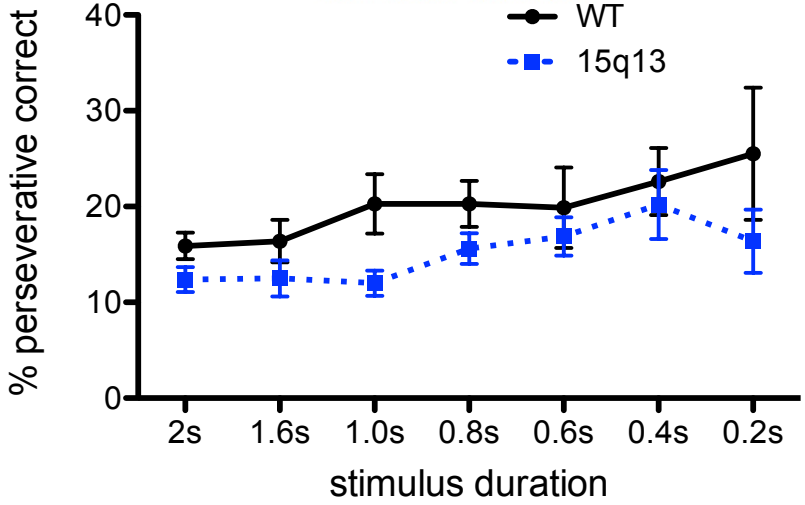
No effect of genotype

15q13 – decreasing stimulus duration
(Test day: 37-68, Animal age: 17 – 22 weeks)



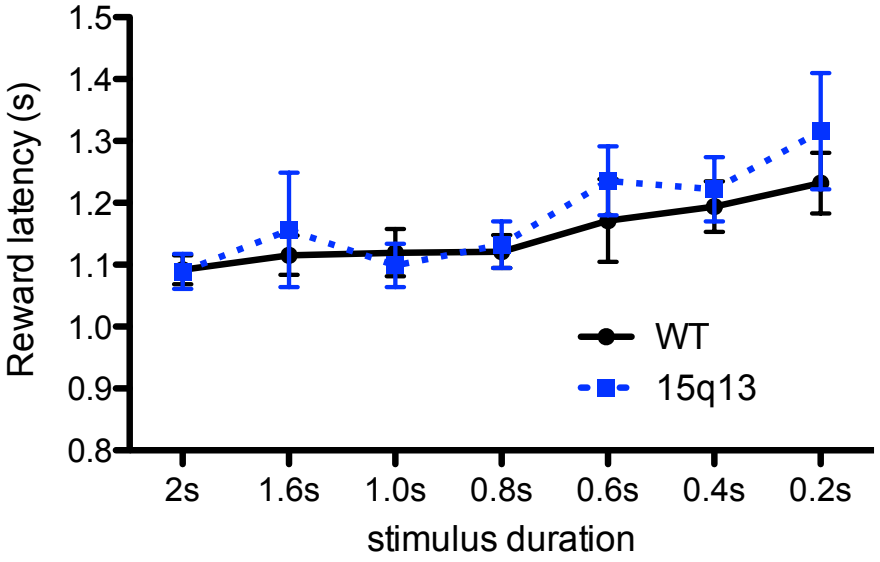


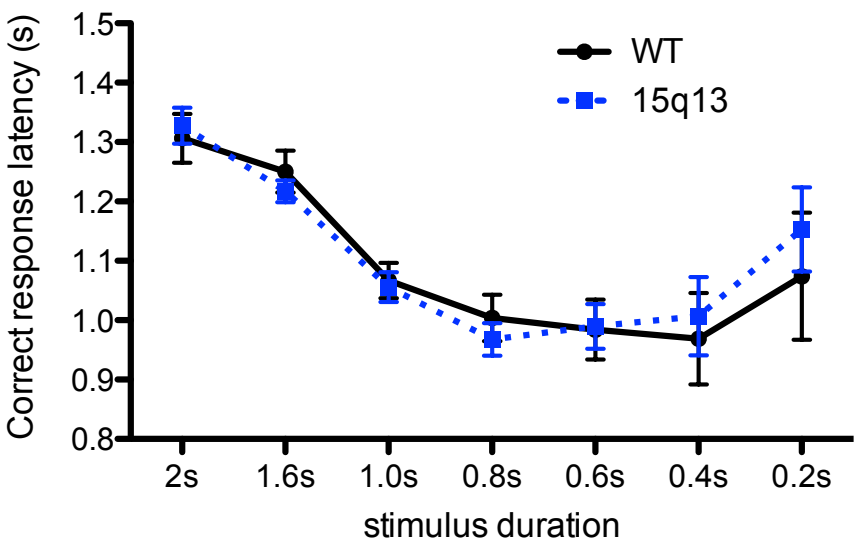




No effect of genotype

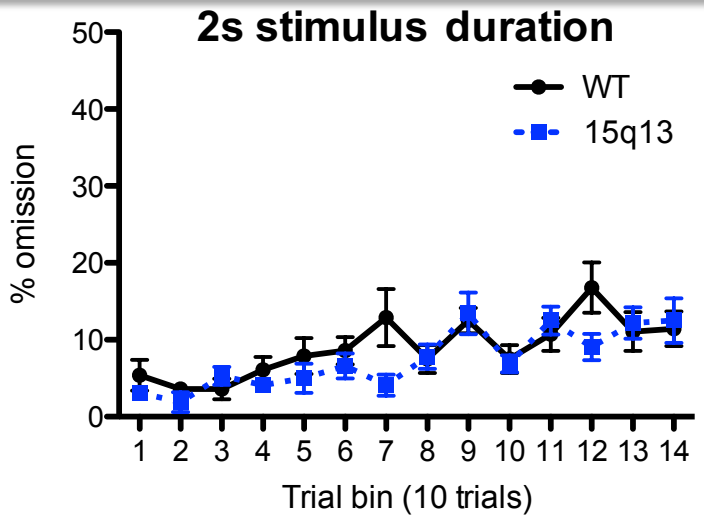
15q13 – decreasing stimulus duration

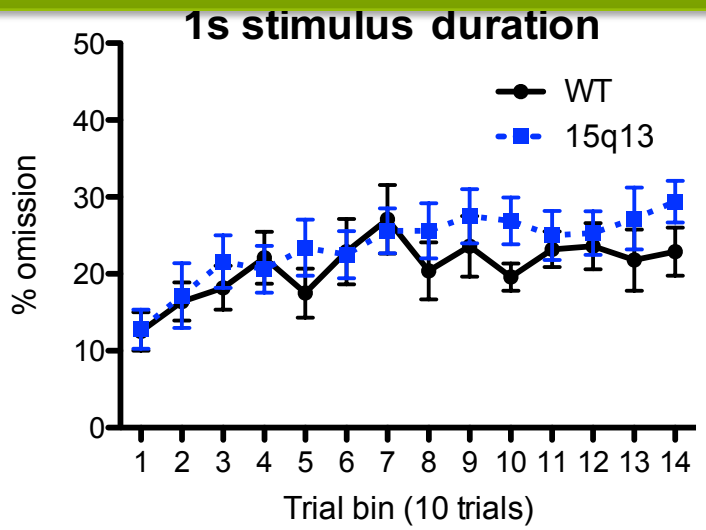


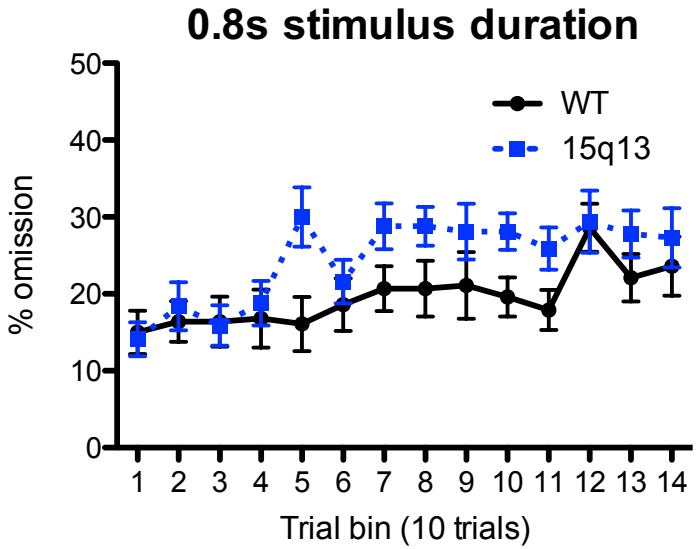


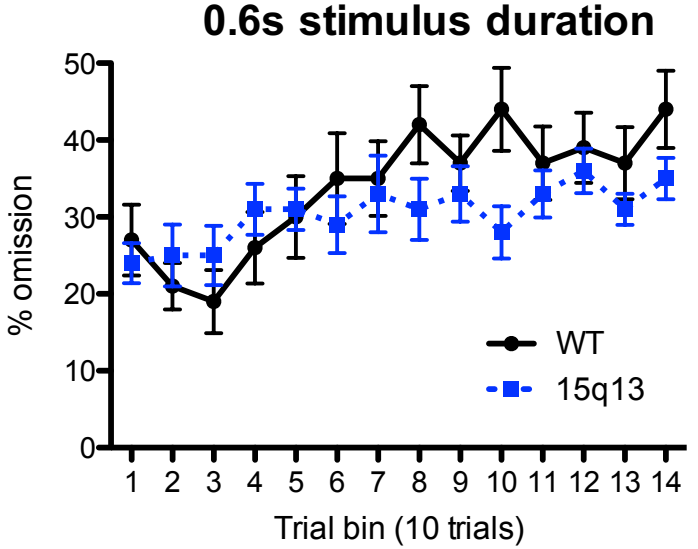
No effect of genotype

15q13
Omissions over 140 trials



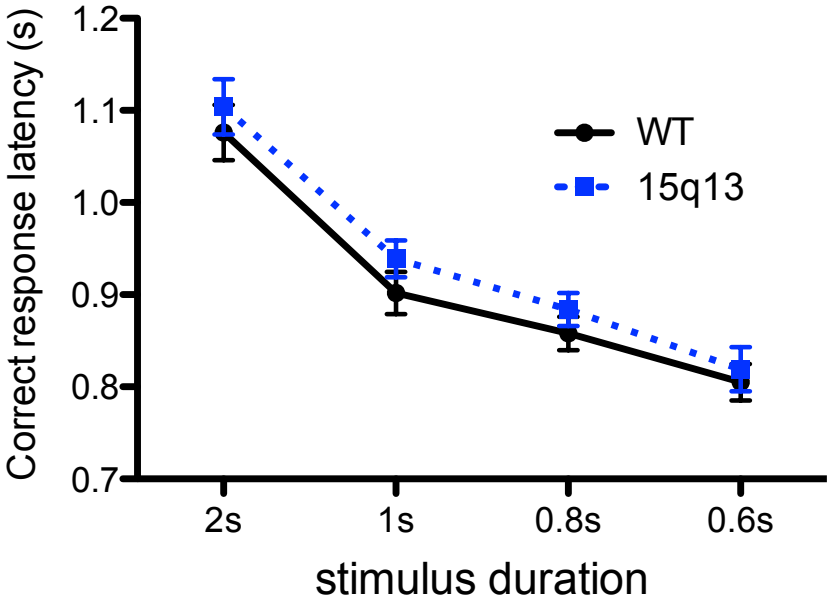


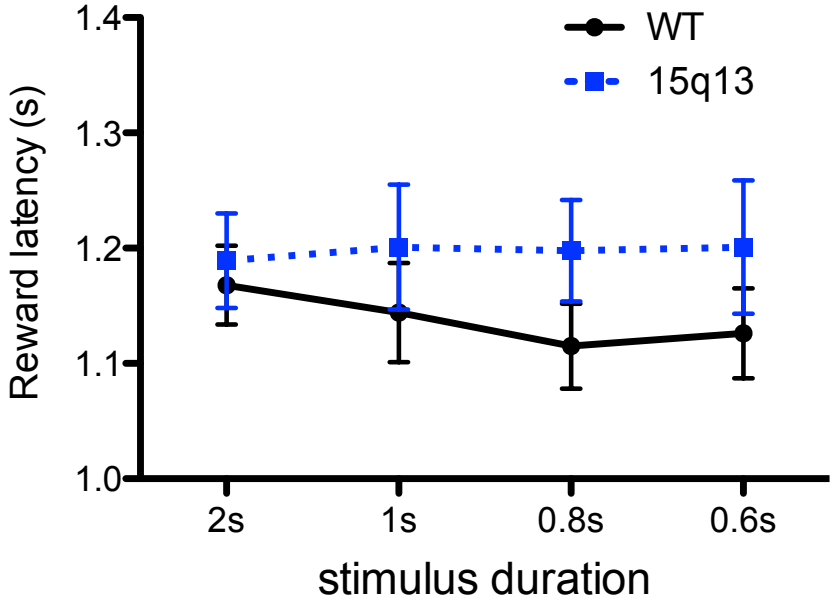




Increase in omissions across trial. No effect of genotype

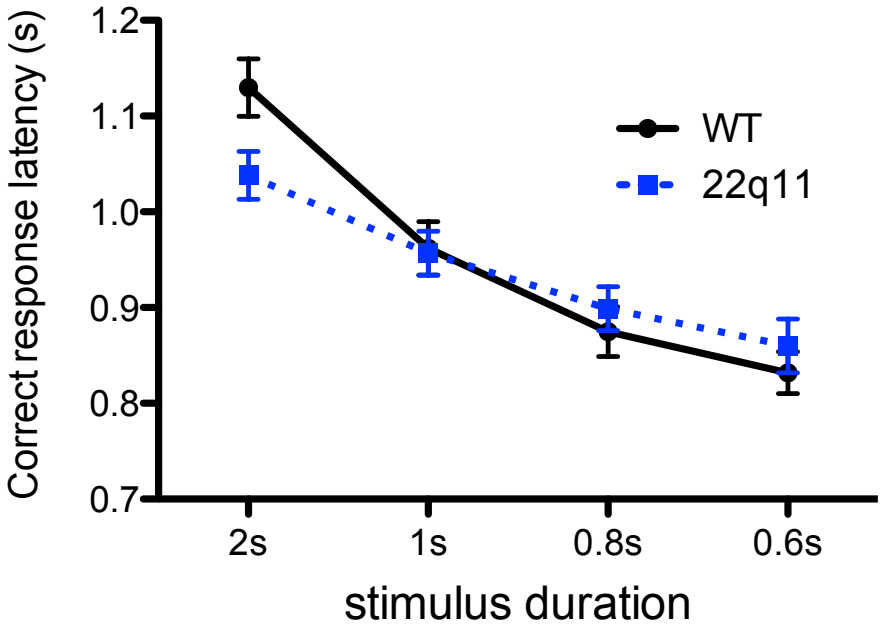
15q13
Latencies - 140 trials

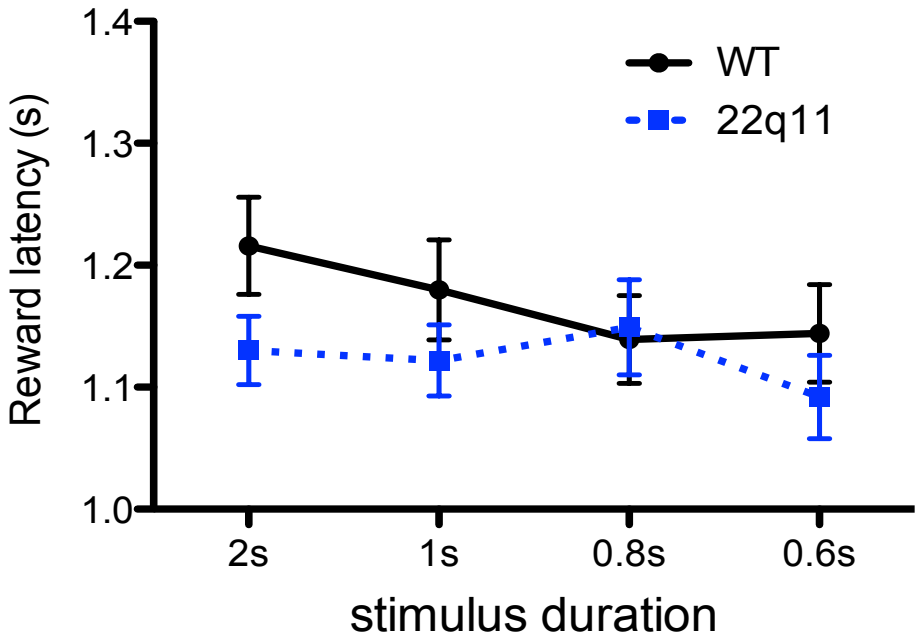




No effect of genotype

22q11
Latencies over 140 trials

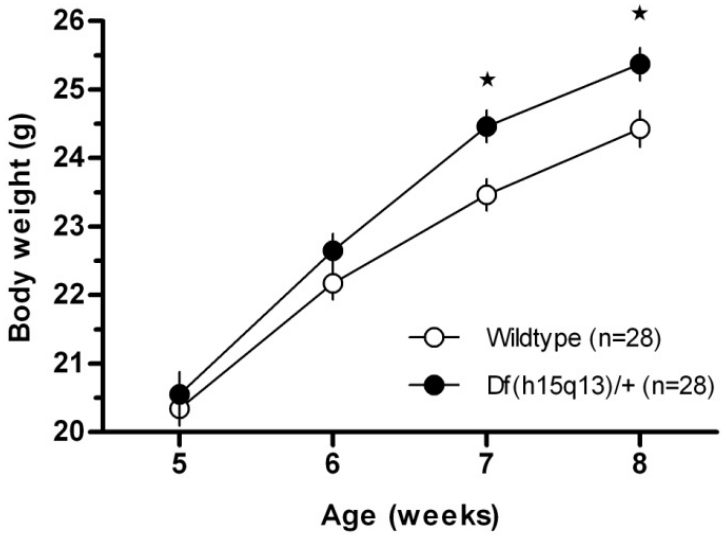


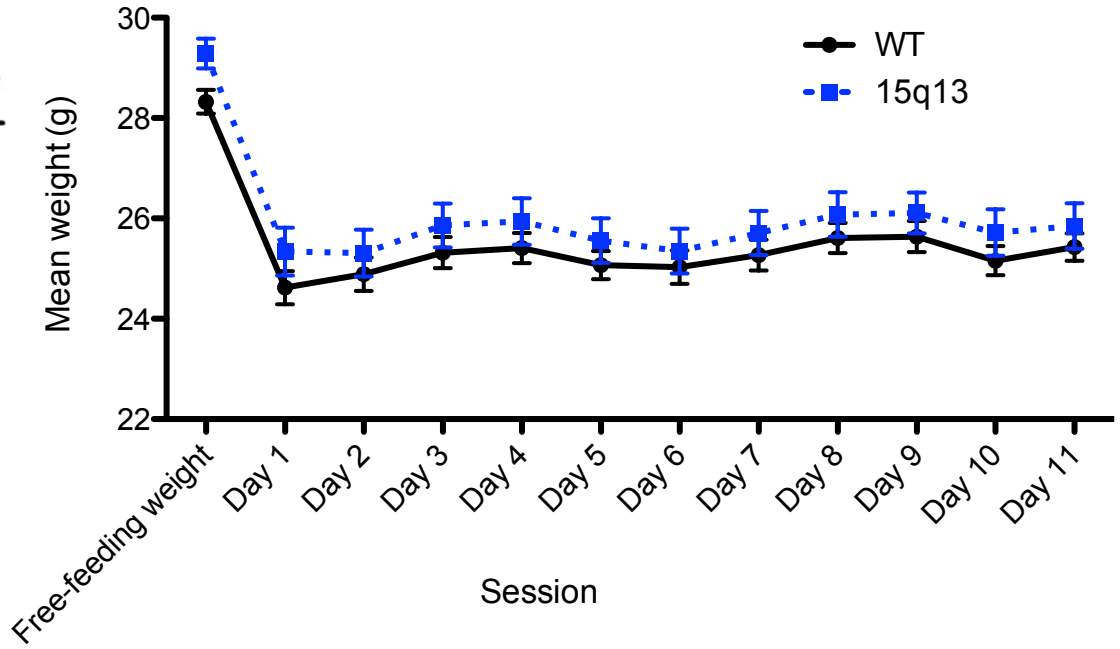


No effect of genotype

15q13
Weights - 140 trial sessions

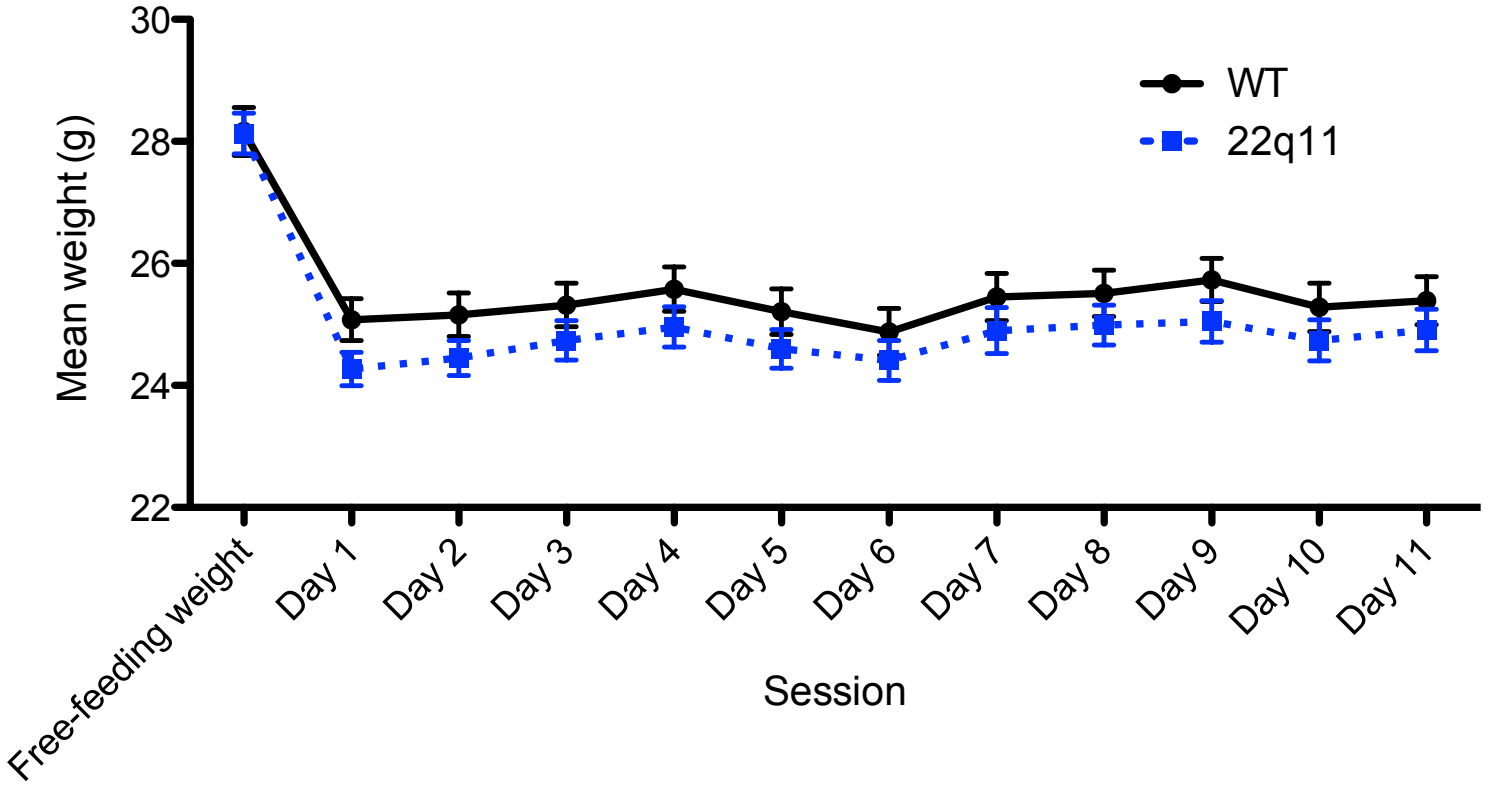
Lundbeck, NEWMEDS, Paris 2012





No sig. effect of genotype on weight during food deprivation

22q11
Weights - 140 trial sessions

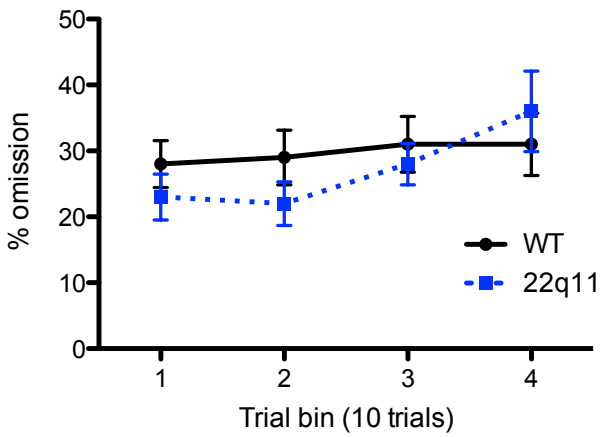


No sig. effect of genotype on weight during food deprivation

Omission 0.8s SD at 40, 80, and 140 trials

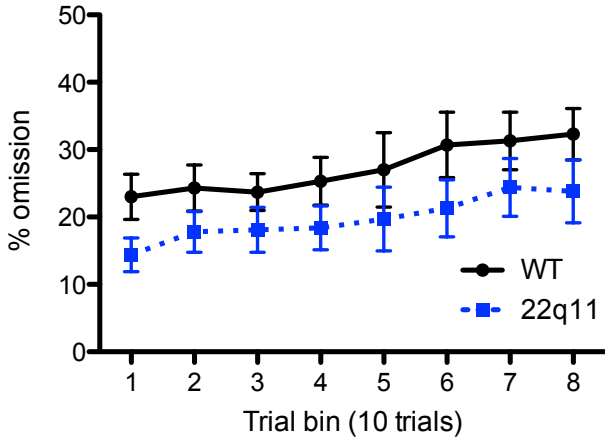
22q11

40 trials



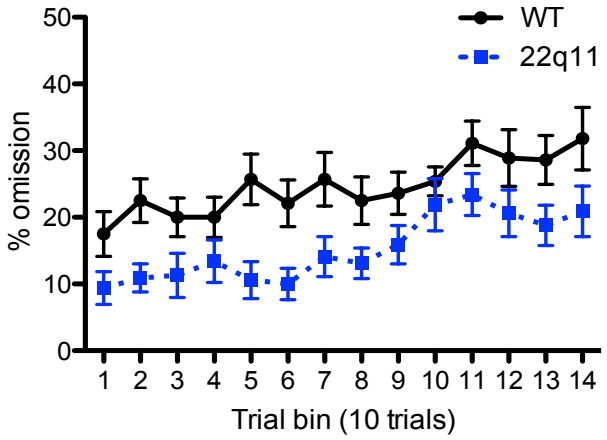
Test day ≈ 54
Animal age: 19 weeks

80 trials



Test day ≈ 92
Animal age: 25 weeks

140 trials



Test day ≈ 105
Animal age: 27 weeks