Emotional and cognitive profiling of *mdx52* and *mdx^{5cv}* mouse models of Duchenne muscular dystrophy

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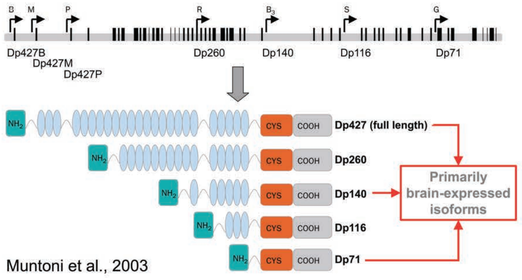
Brain-expressed dystrophin isoforms and mouse models of DMD: *mdx^{5cv}* and *mdx52* mutations



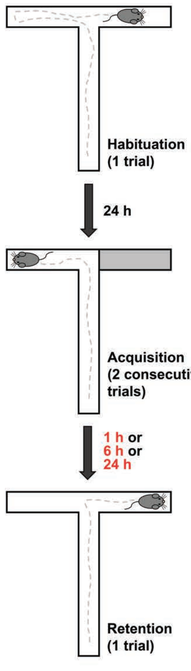
Muntoni et al., 2003

Mouse	Dp427	Dp140	Dp71
mdx23	×	✓	✓
mdx^{5cv}	×	✓	✓
mdx^{2cv}	×	✓	✓
mdx52	×	×	✓
mdx^{4cv}	×	×	✓
mdx^{3cv}	×	×	×
Dp71-null	✓	✓	×
DMD-null	×	×	×

Goal: characterise emotional and cognitive deficits associated with loss of Dp427 versus loss of Dp427 & Dp140; assess phenotype robustness by testing in two different labs
- **Paris-Saclay Institute of Neuroscience, France (CNRS/UVSQ)**
- **Transpharmation Ireland Limited, Ireland (TIL)**

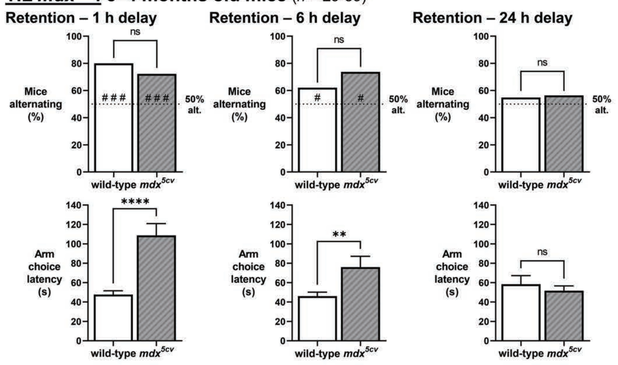
mdx^{5cv} and *mdx52* mice do not demonstrate spatial reference memory deficits

T-maze delayed alternation test: 5 min maximum trial duration, automated operation

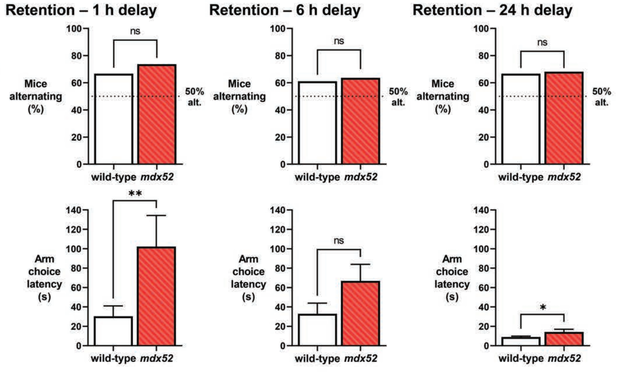


TIL *mdx^{5cv}*: 3–4 months old mice (*n* = 29-39)

= comparison to 50% alternation



CNRS/UVSQ *mdx52*: 3 months old mice (*n* = 18-22)



mdx^{5cv} and *mdx52* mice present enhanced anxiety-like behaviours & unconditioned fear responses

Elevated zero maze test: 5 min duration, start in closed area, automated tracking

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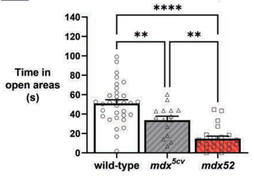
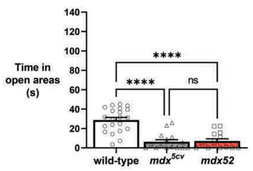
TIL: 6–7 weeks old mice (*n* = 15-32)



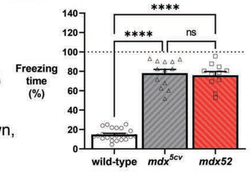
TIL: 3–4 months old mice (*n* = 14-21)



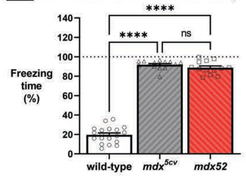
Unconditioned fear response test: 15 s restraint, 5 min open field observation, automated tracking

Donovan & Brown, 2006

TIL: 6–7 weeks old mice (*n* = 11-23)

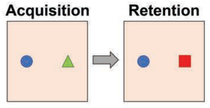


TIL: 3–4 months old mice (*n* = 13-19)



mdx^{5cv} and *mdx52* mice display subtle recognition memory impairments

Novel object recognition test: 3x 5 min acquisition trials, ITI 2 min; 1x 5 min retention trial

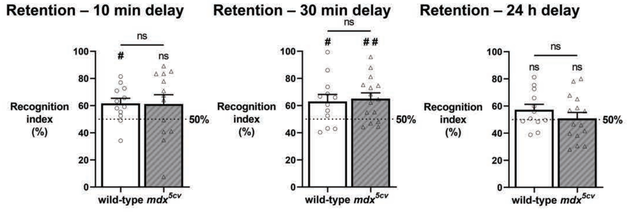


Recognition index:

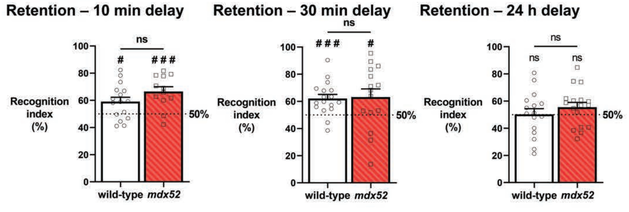
$$\frac{\text{Novel object exploration time}}{\text{Total objects exploration time}} \%$$

= comparison to 50% (chance level)

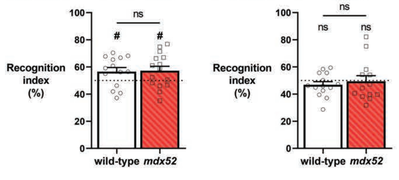
TIL *mdx^{5cv}*: 3–4 months old mice (*n* = 12-15)



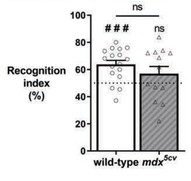
TIL *mdx52*: 3–4 months old mice (*n* = 12-17)



CNRS/UVSQ *mdx52*: 3 months old mice (*n* = 13-15)

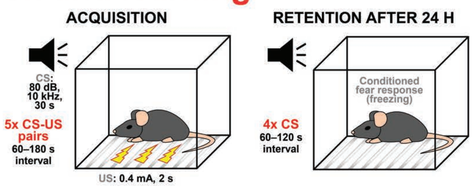


CNRS/UVSQ *mdx^{5cv}*: 3 months old mice (*n* = 13-15)

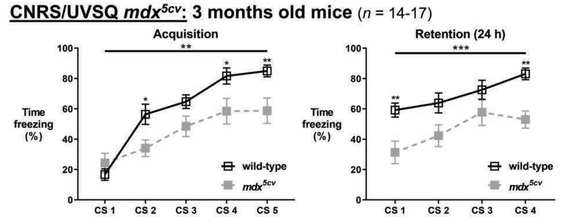


mdx^{5cv} and *mdx52* mice show impaired fear-related cognition and learning

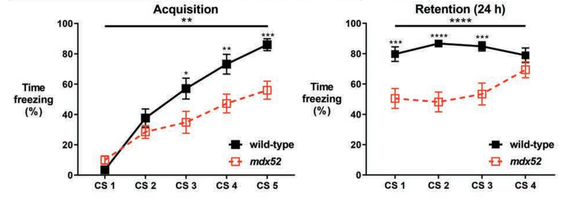
Auditory-cued fear conditioning test: freezing measured during CS presentation



CNRS/UVSQ *mdx^{5cv}*: 3 months old mice (*n* = 14-17)



CNRS/UVSQ *mdx52*: 3 months old mice (*n* = 16-18)



Conclusions

- Both **proximal** (*mdx^{5cv}*) **& distal** (*mdx52*) ***Dmd* mutations** result in:
  - **enhanced unconditioned fear responses**
  - **heightened anxiety**
  - **impaired amygdala-dependent associative learning**
- **Higher anxiety in young *mdx52* versus *mdx^{5cv}* mutants**
  → Parallels correlation of **worse neuropsychological deficits** with human mutations affecting **multiple brain-expressed dystrophin isoforms** (Banihani et al., 2015; Felisari et al., 2000)
- Genotype differences in unconditioned fear responses robustly persist with retesting, whereas **anxiety-like behavioural assays** are **susceptible to prior exposure effects**
  → **Limitation in applicability to longitudinal *in vivo* studies**
- **Recognition memory impairments** observed in *mdx^{5cv}* and *mdx52* mice are **less pronounced than those reported in *mdx23* mice**, and **less reproducible** across labs
  → **Possible effect of genetic background** (C57BL/6 versus C57BL/10)

Emotional reactivity, anxiety-like behaviours & fear learning
=
potential neurobehavioural readouts in preclinical & clinical research on brain-targeted dystrophin restoration therapies

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