

SfN Neuroscience 2021 meeting

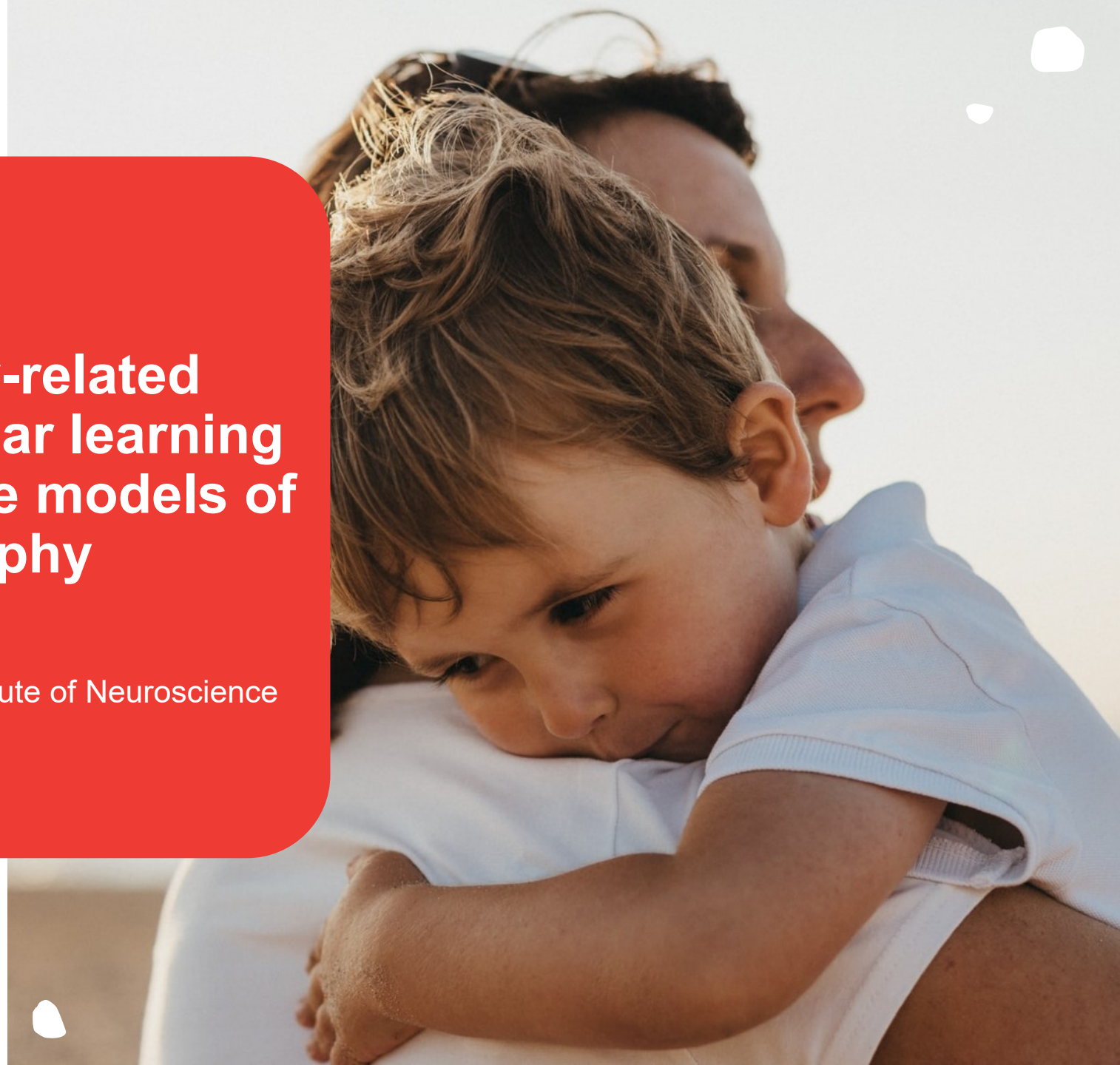
Enhanced fear- and anxiety-related behaviours and impaired fear learning in *mdx52* and *mdx*^{5cv} mouse models of Duchenne muscular dystrophy

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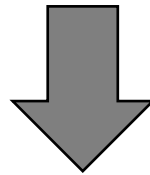
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Brain function in Duchenne muscular dystrophy (DMD)

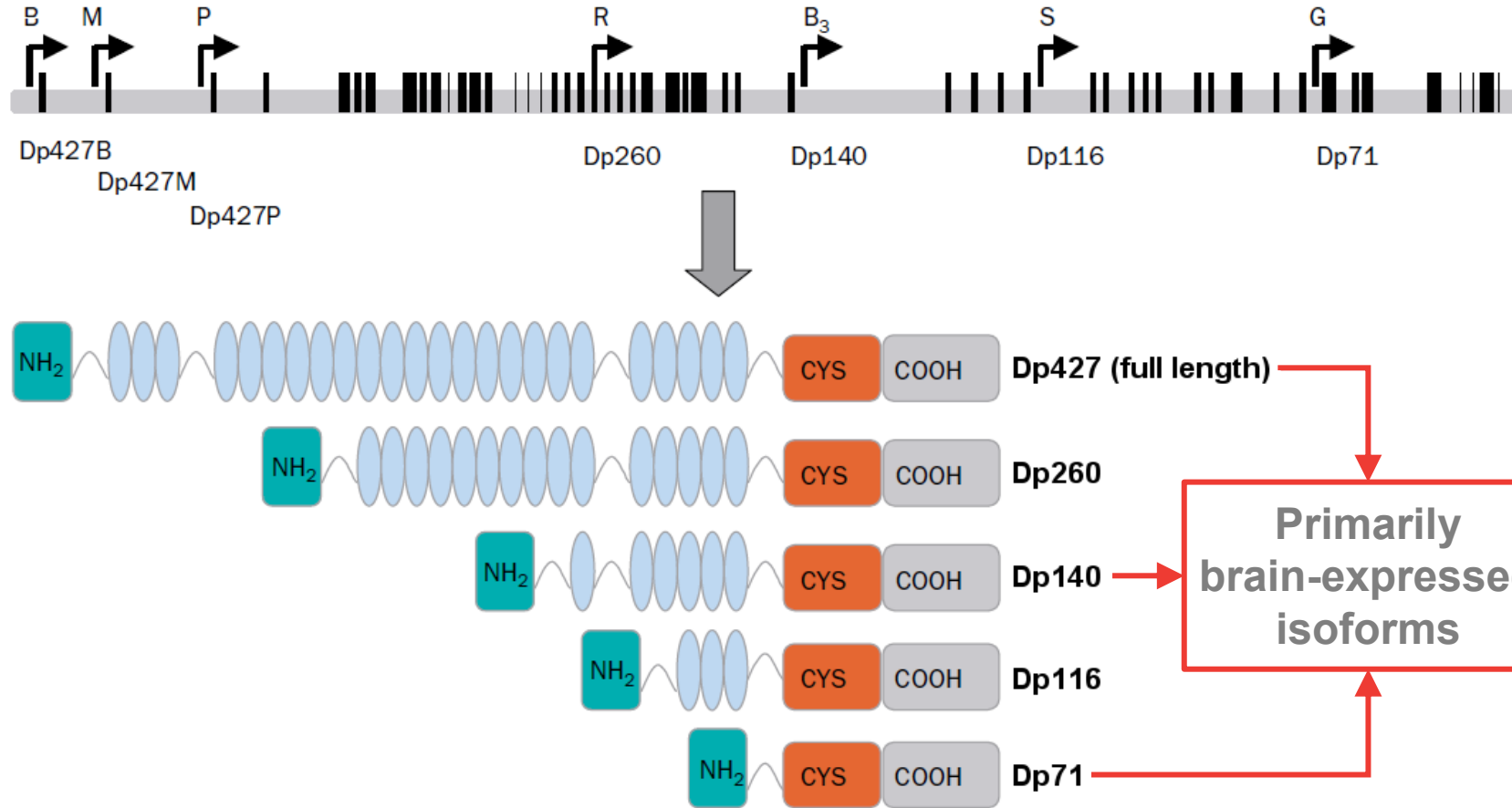
- Duchenne muscular dystrophy: X-linked recessive disorder caused by mutations in the **dystrophin (*DMD*) gene**, resulting in the loss of functional protein production
- DMD main feature: progressive muscle fibre degeneration; **high prevalence of brain-related comorbidities**, frequently co-occurring (Banihani et al., 2015; Cotton et al., 2001; Hendriksen & Vles, 2008; Hendriksen et al., 2018; Pane et al., 2012; Ricotti et al., 2016; Steele et al., 2008)
 - Psychiatric symptoms reported in up to 50% of affected individuals
 - Most common neurodevelopmental and neuropsychiatric comorbid conditions: ADHD, anxiety disorders, learning disabilities, intellectual disability, autism, depression, epilepsy, OCD
- In a pilot study of 31 DMD and 25 control boys, DMD children demonstrated exaggerated fear responses to an unconditioned 'threat' stimulus in a bespoke fear conditioning task (Maresh et al., 2021)



Study aim:
**assess emotional reactivity, anxiety-like behaviours, and fear-related cognition
in mouse models of DMD**



Brain-expressed dystrophin isoforms and DMD mouse models



Muntoni et al., 2003

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

mdx^{5cv} and *mdx52* mice present an hyperanxious behavioural profile (I)

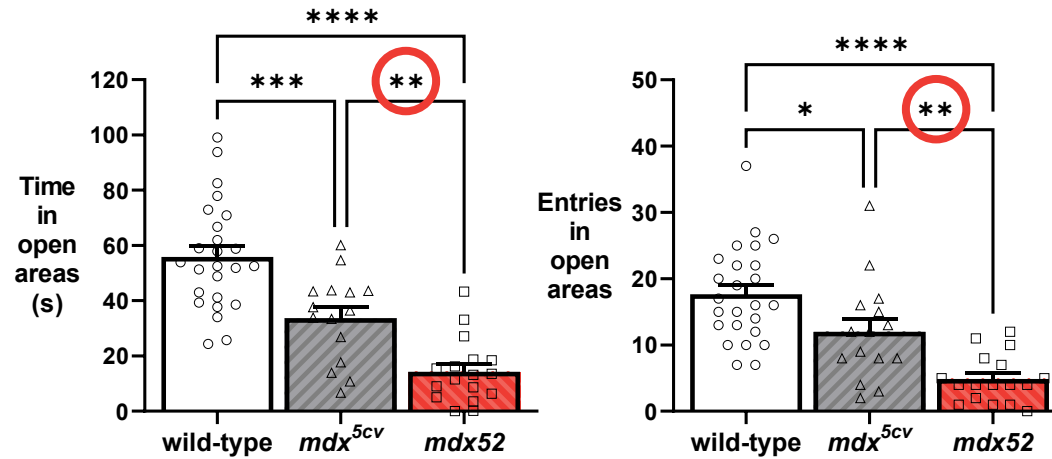
Elevated zero maze test 5 min test, start in closed area



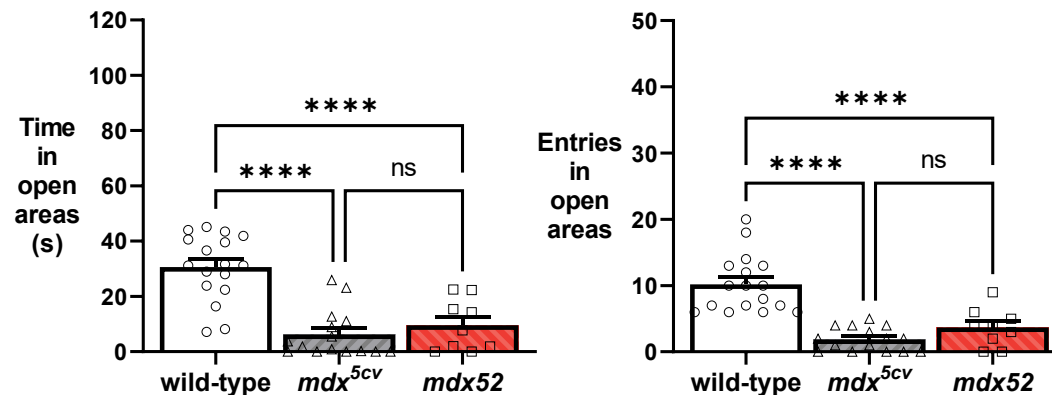
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Data by M. Mitsogiannis,
E. Stojek, S. Talavera,
E. Sokolowska

6–7 weeks old mice (*n* = 15-25/group)



3–4 months old mice (*n* = 9-17/group)

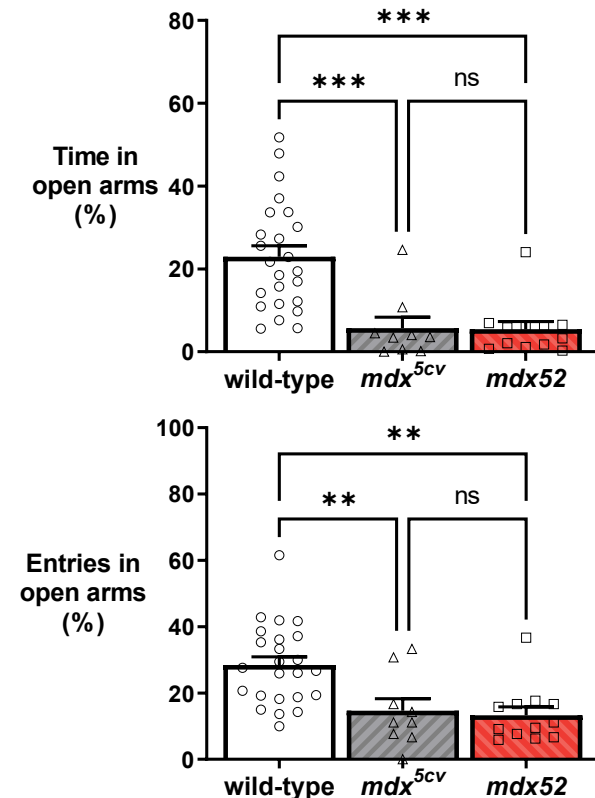


Elevated plus maze test

5 min test, start in centre arena facing closed arm



2 months old mice (*n* = 9-24/group)



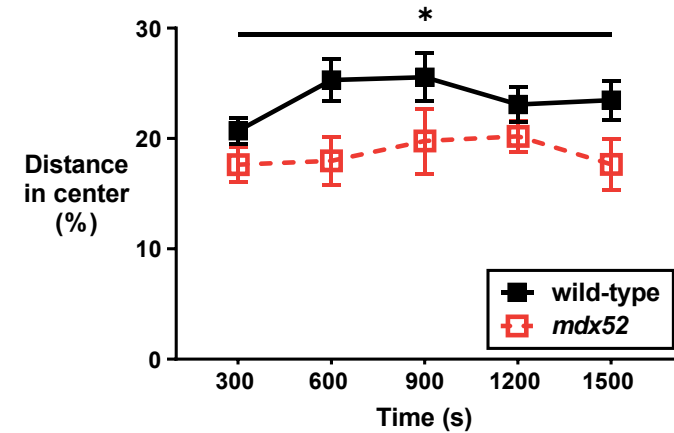
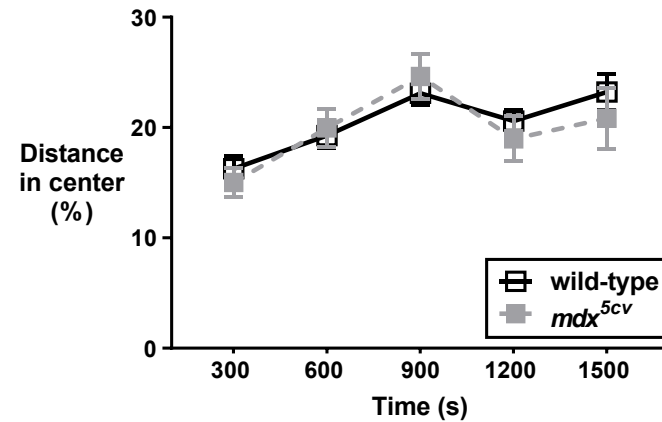
Data by A. Saoudi,
C. Vaillend

mdx^{5cv} and *mdx52* mice present an hyperanxious behavioural profile (II)

Open field exploration

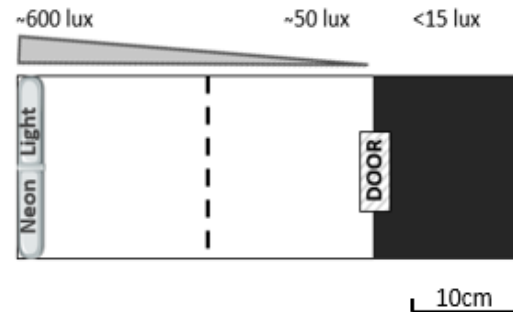
square open field (50×50×50 cm),
black walls, sawdust-covered floor

2 months old mice (*n* = 10-17/group)

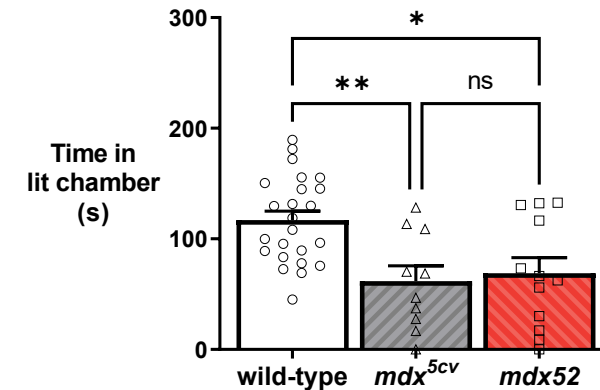
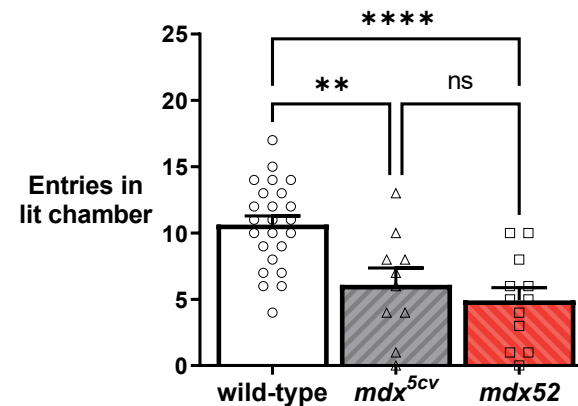


Light-dark choice test

5 min test, start in dark
chamber (10 s confinement)



2 months old mice (*n* = 10-24/group)



mdx^{5cv} and *mdx52* mice show enhanced unconditioned fear responses

Unconditioned fear response test

15 s restraint, 5 min open field
(28×28 cm) observation

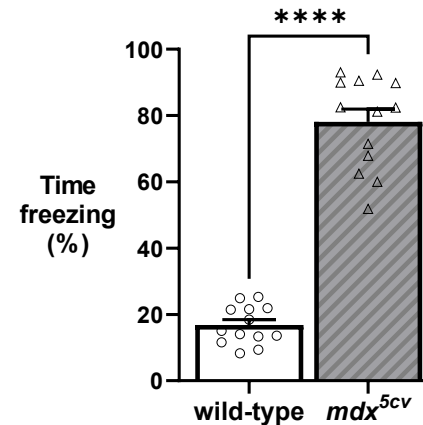


Donovan & Brown, 2006

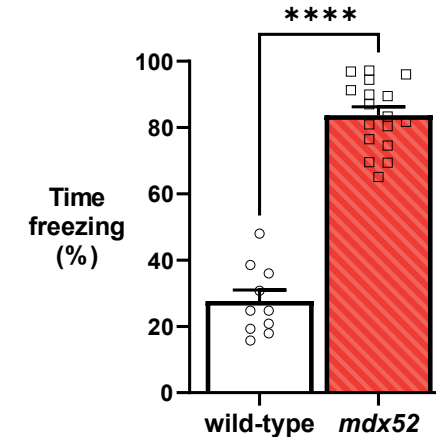
mdx^{5cv}: video-based tracking
mdx52: IR photobeam-based
tracking

Data by M. Mitsogiannis, E. Stojek,
S. Talavera, E. Sokolowska

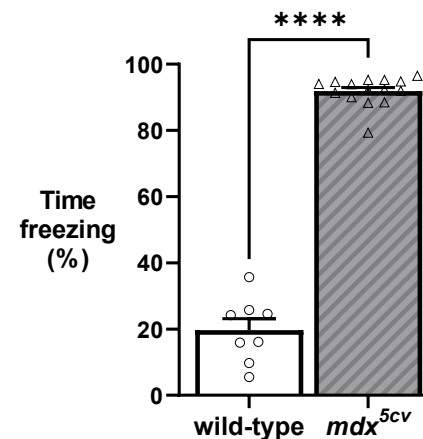
mdx^{5cv}: 6–7 weeks old mice
(*n* = 13/group)



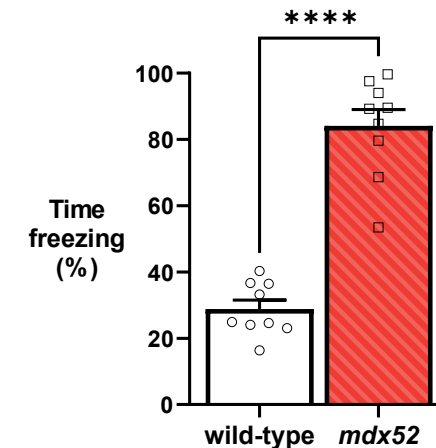
mdx52: 6–7 weeks old mice
(*n* = 10-17/group)



mdx^{5cv}: 3–4 months old mice
(*n* = 8-15/group)

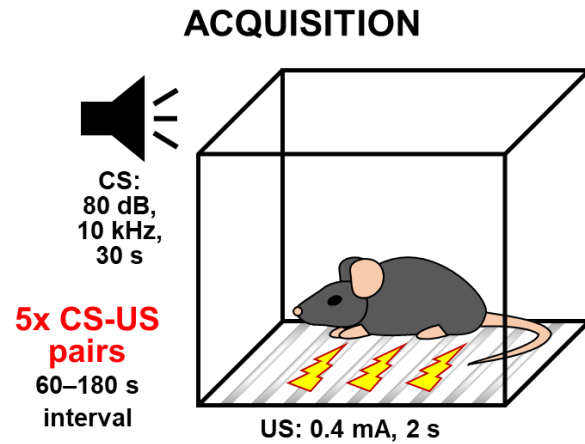


mdx52: 3–4 months old mice
(*n* = 9/group)

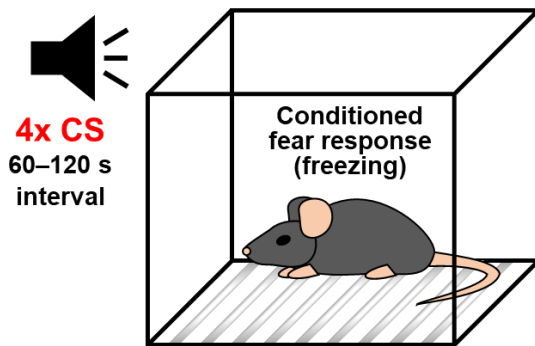


mdx^{5cv} and *mdx52* mice demonstrate impaired fear learning

Auditory-cued fear conditioning test

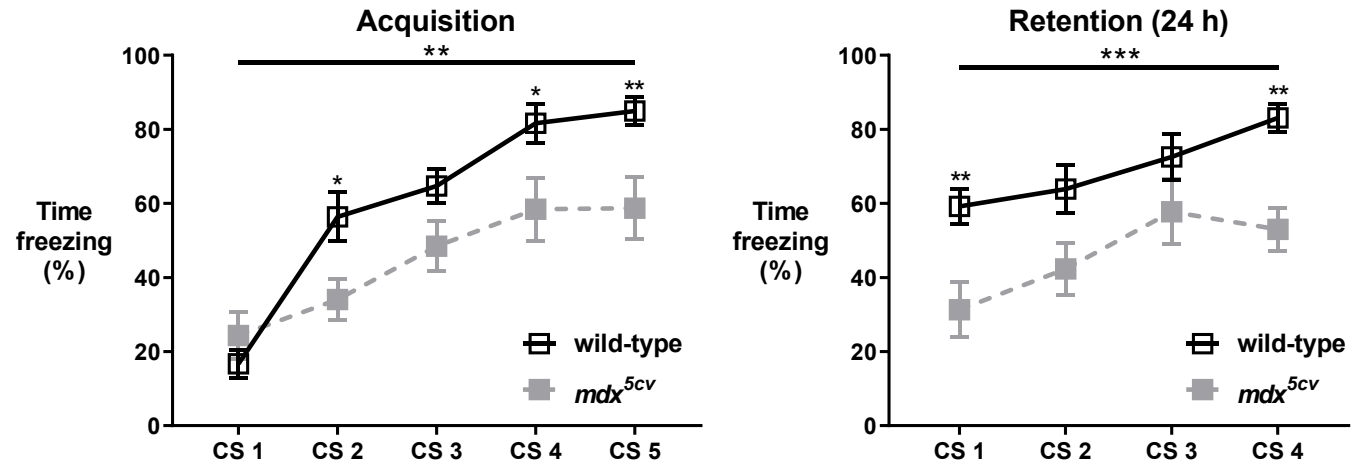


RETENTION AFTER 24 H

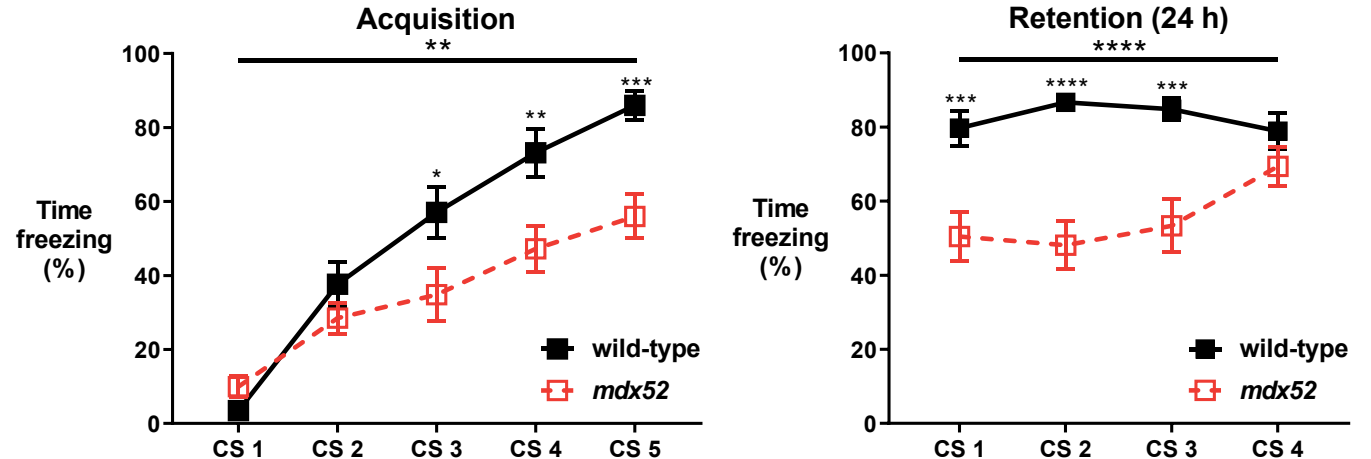


Data by F. Zarrouki, C. Vaillend

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



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





Conclusions

- Both **proximal** (*mdx^{5cv}*) and **distal** (*mdx52*) **Dmd** mutations are associated with
 - **heightened anxiety**
 - **enhanced unconditioned fear responses**
 - **impaired amygdala-dependent associative learning**
- **Higher anxiety in *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)

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



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Association
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Thank you for your attention!

**For further information on the BIND project
please visit <https://bindproject.eu/>**

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