Characterisation of touch and pain behavioural phenotype in an Fmr1$^{-/y}$ rat model of Fragile X Syndrome

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Background

Fragile X Syndrome (FXS) is the most common cause of monogenic inherited intellectual disability and autism spectrum disorder (ASD) (1). Altered sensitivity to sensory stimuli, including tactile hypersensitivity, is frequently observed in ASD (2,3). Touch and pain sensitivity alterations have also been reported in FXS mouse models (4-6). A novel rat model of FXS with knock-out of the *FMR1* gene (Fmr1$^{-/y}$) has been developed, providing an alternative tool to study somatosensation in ASD.

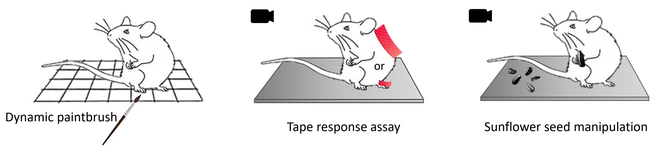
Aim

Assess tactile and nociceptive behavioural phenotype in an Fmr1$^{-/y}$ rat model

Methods

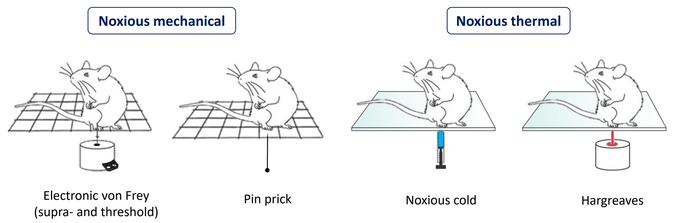
Animals – All experiments were carried out in accordance with the UK Animals (Scientific Procedures) Act 1986 and IASP ethical guidelines for animal research. Adult male Fmr1$^{-/y}$ (n=9) and wild-type (n=9) rats were used for all experiments.

Tactile sensitivity – Non-noxious tactile sensitivity of the glabrous skin was assessed using paintbrush stroking of the plantar surface of the hindpaw and scoring the response (0-3, average of 3 stimuli). Sunflower seed manipulation assay was also used, where 10 seeds were placed in a test chamber and seed deshelling behaviours were video-recorded and scored. Tactile sensitivity of the hairy skin was measured using tape response assay, where a piece of tape was applied to the back or hindpaw of the rat and its behaviour video-recorded for 5 minutes and scored.



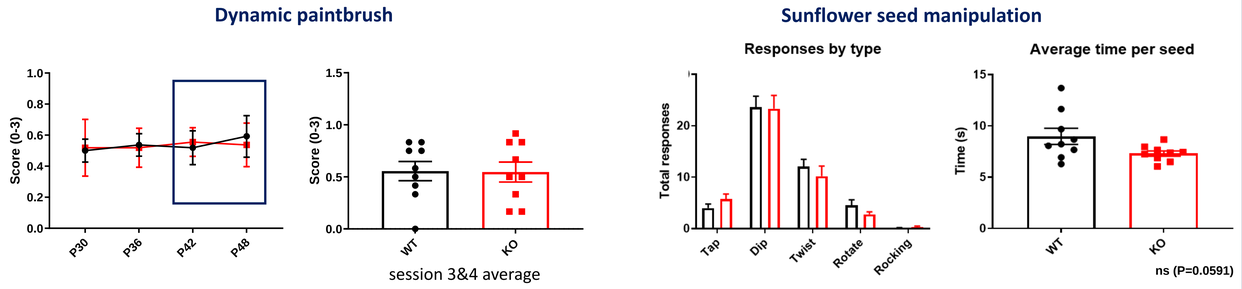
Noxious mechanical sensitivity – Electronic von Frey was used to quantify the mechanical threshold (25 g/second ramp to a maximum force of 50 g, average of 3 stimuli). Noxious mechanical sensitivity was measured using suprathreshold electronic von Frey (50 g/second ramp to a maximum force of 50 g) and pin prick assay, where a blunted 23 gauge needle is applied to the plantar surface of the hindpaw without breaking the skin and response scored (0-5).

Noxious thermal sensitivity – Hargreaves apparatus was used to measure noxious heat sensitivity by applying radiant heat to the plantar surface of the hindpaw and recording the withdrawal latency (average of 3 stimuli). To measure noxious cold sensitivity, a pellet of dry ice crushed within a syringe is applied to the glass surface beneath the plantar aspect of hindpaw and the withdrawal latency recorded (average of 3 stimuli).



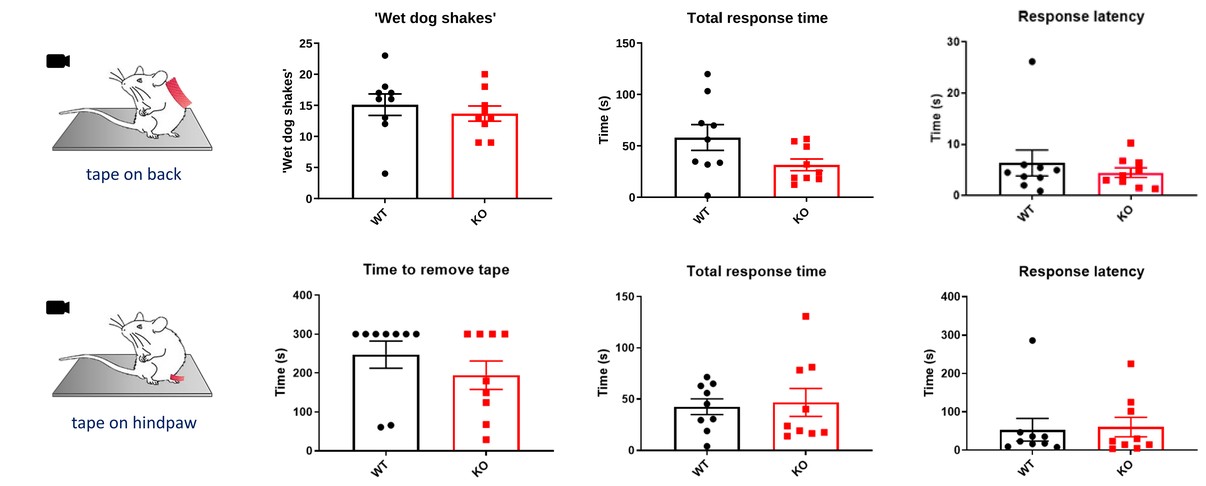
Analysis – Each behavioural measure was tested on 4 sessions, sessions 3 and 4 were averaged (tape response, seed manipulation – 1 session each). Graphad Prism 7 software was used for statistical analysis and graph production. BORIS software was used for scoring of video recordings. Statistical analysis was carried out using unpaired t-test, Mann-Whitney test or two-way repeated measures ANOVA with Sidak's multiple comparisons test. All data are represented as mean ± standard error of the mean (SEM), *p<0.05; ns - non-significant.

Tactile sensitivity of glabrous skin



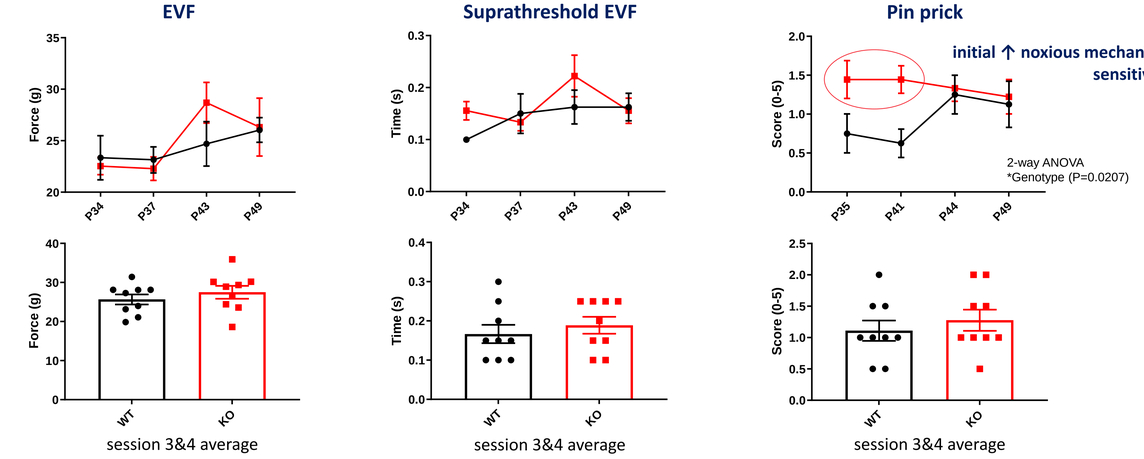
unaltered tactile glabrous skin sensitivity

Tactile sensitivity of hairy skin



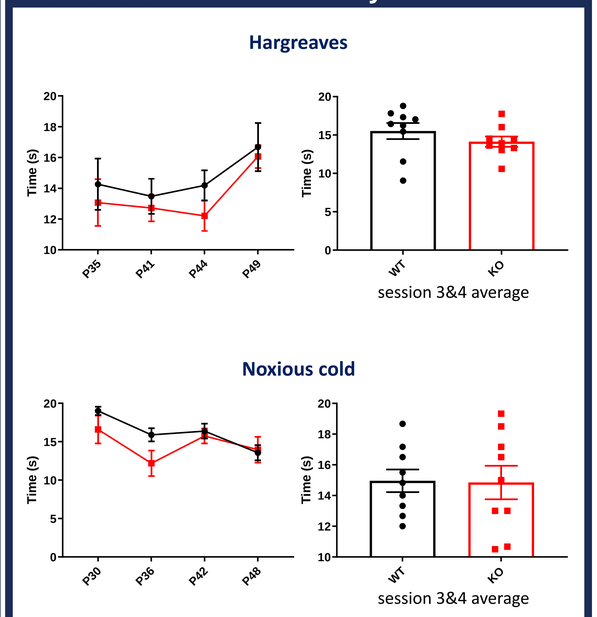
unaltered tactile hairy skin sensitivity

Noxious mechanical sensitivity



unaltered late mechanical sensitivity

Noxious thermal sensitivity



unaltered thermal sensitivity

Conclusion

Tactile and pain sensitivity is largely unaltered in the Fmr1$^{-/y}$ rat model of Fragile X Syndrome. Evidence for noxious pin prick hypersensitivity is inconclusive.

The hypersensitivity observed in initial sessions could reflect a developmental hypersensitivity or poor test acclimatisation.

Relevance for patient care

Fmr1$^{-/y}$ rat model can be complementary to future studies of somatosensation in other preclinical ASD models, giving potential insight into mechanisms underlying altered touch and pain sensitivity in ASD.

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References

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