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Journal of Neurodevelopmental Disorders (2021) 13:59
https://doi.org/10.1186/s11689-021-09409-7

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

MeCP2 haplodeficiency and early-life stress interaction on anxiety-like behavior in adolescent female mice

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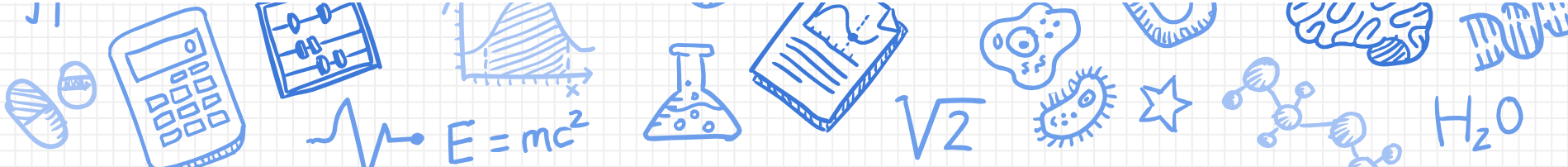


Introduction: Early life stress

- ✘ Objective:
  - ✗ Analysis of correlation between ELS and development of future psychiatric conditions (Anxiety, Depression, Stress)
- ✘ Conclusion: ELS is major risk factor
  - ✗ Adverse events during this period of development permanently alter epigenetic markers
  - ✗ Effect regulation of stress response in future

Introduction: MeCP2

- Objective:
  - Analysis of correlation between MeCP2 and development of future psychiatric conditions (Anxiety, Depression, Stress)
- MeCP2: Protein that assists in transcriptional regulation, epigenetic programs, mircoRNA processing and chromatin remodeling
- In Human System: Key Role in facilitating many biological processes relating to neuron gene expression
  - CRH (Corticotropin-releasing hormone)
  - AVP (Arginine Vasoprestine)
    - Both control secretion of corticosteroids(stress-regulating hormone)
- Correlation between MeCP2 and Neurodevelopmental diseases

Introduction: Connecting ELS and MeCP2 deficiency

- Analysis of connection/similarities between
  MeCP2 deficiency and ELS

Results suggest these factors result in similar increased vulnerability development of future psychiatric conditions

Hypothesized that this might suggest that ELS is a MeCP2 dependant process

Introduction: Rett syndrome (RTT)

Caused by MeCP2 mutations and deficiency

Symptoms: loss of speech, intellectual disability, repetitive behavior, autistic features, altered anxiety behavior

Individuals also show reduced cortisol concentration in bloodstream

Exhibit high anxiety and depression phenotypes

Primary research question

Does MeCP2 deficiency and early-life stress interact with the development of abnormal anxious responses through dysfunctional epigenetic programming of the HPA axis?

Methods

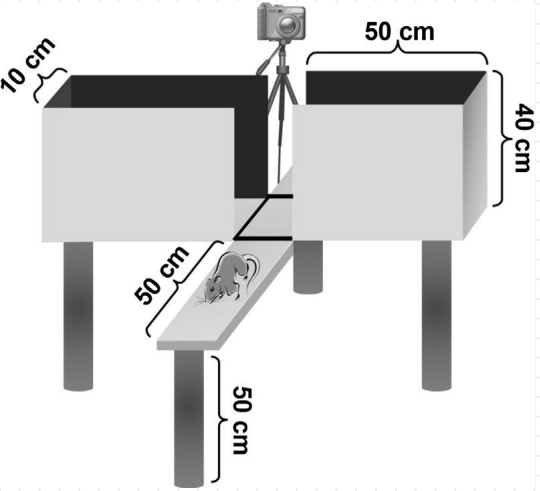
Groups: MeCP2 deficiency mice (*MeCP2*.het) vs. wild-type

Treatment: maternal separation vs. no maternal separation

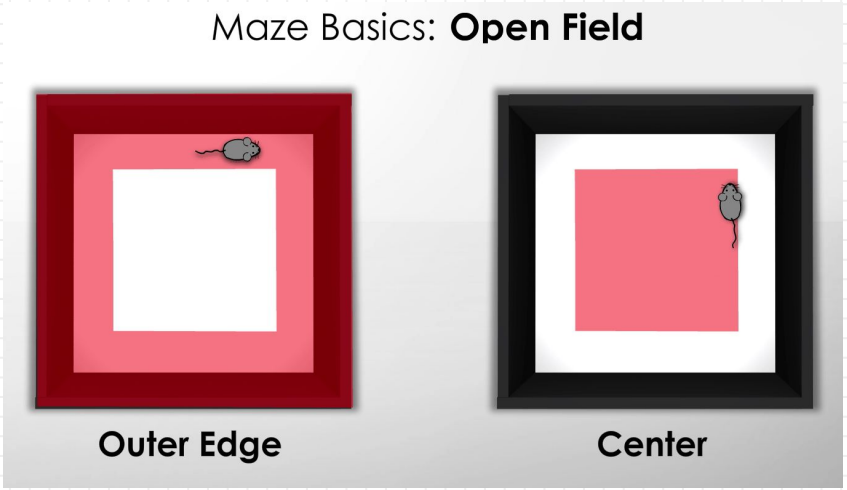
Measures:

- Anxiety-like behaviors: elevated plus maze, open field
- Depression-like behaviors: forced-swim test

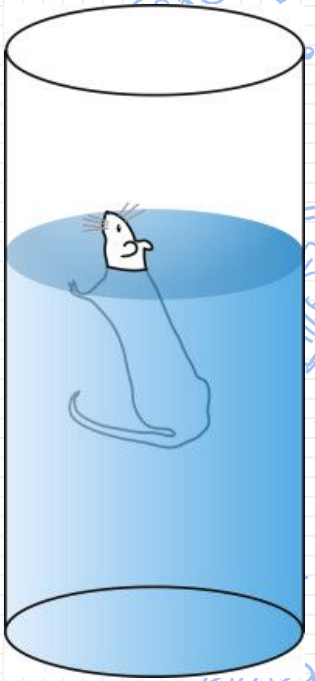
Behavioral measures



Elevated-plus maze



Open-field test



Forced-swim test

Fig 1

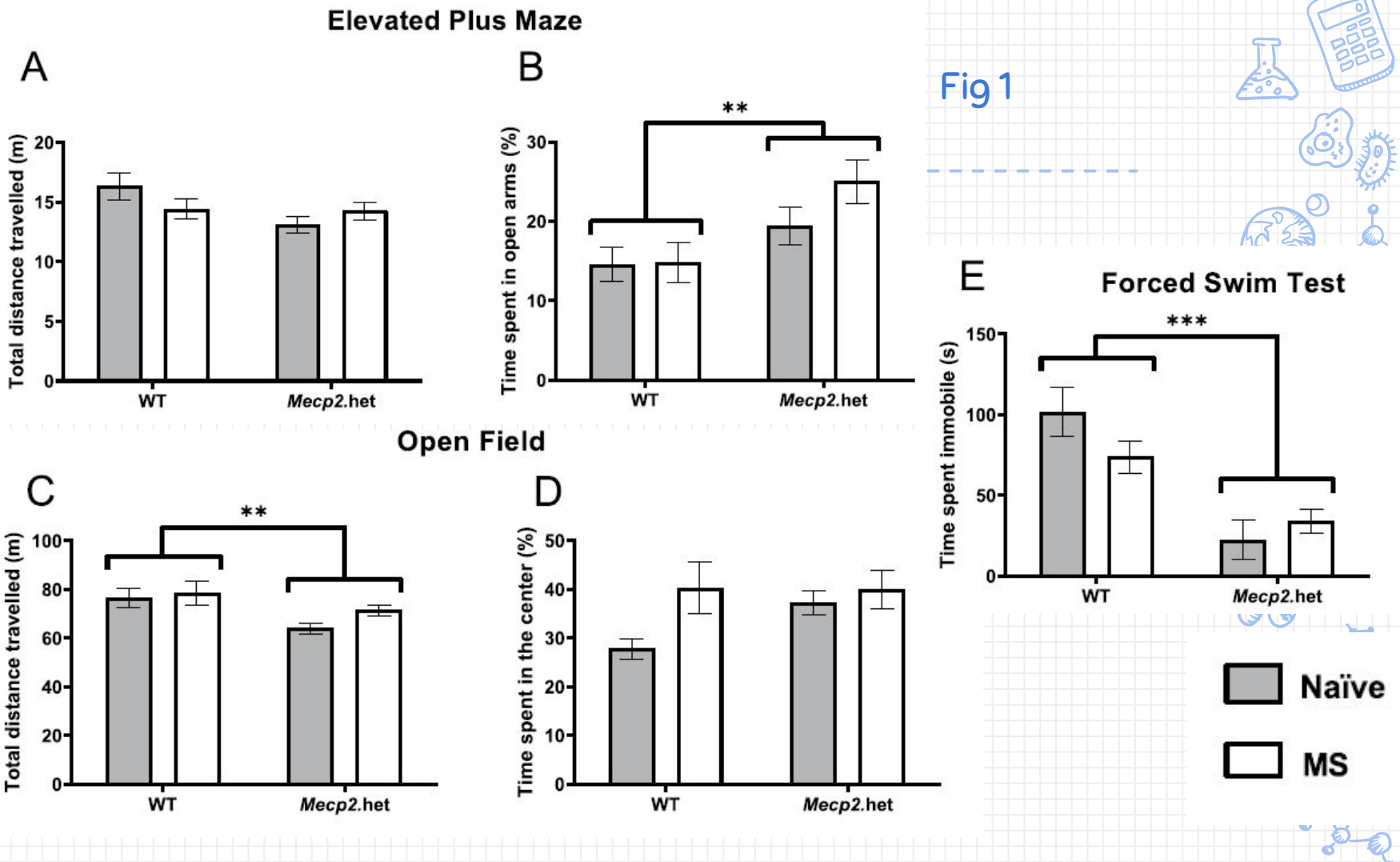
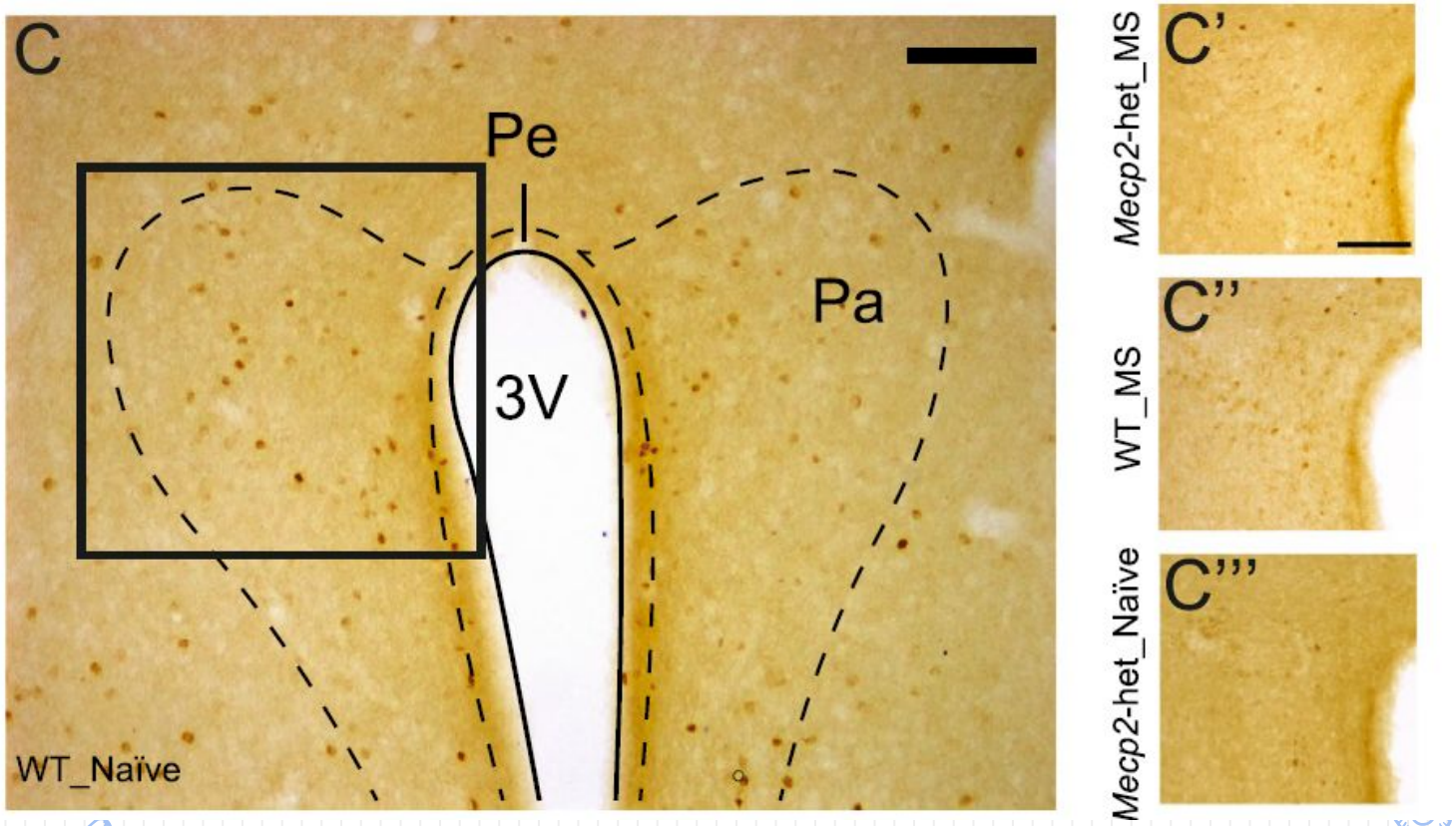
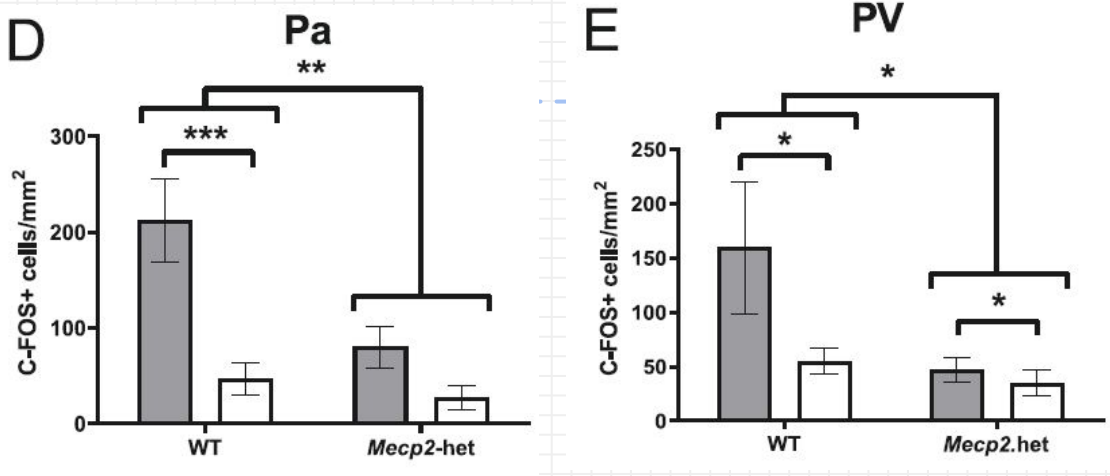

Elevated Plus Maze
A
Total distance travelled (m)
20
15
10
5
0
WT
Mecp2.het
B
Time spent in open arms (%)
**
30
20
10
0
WT
Mecp2.het
Open Field
C
Total distance travelled (m)
**
100
80
60
40
20
0
WT
Mecp2.het
D
Time spent in the center (%)
50
40
30
20
10
0
WT
Mecp2.het
E
Forced Swim Test
Time spent immobile (s)
***
150
100
50
0
WT
Mecp2.het
Naïve
MS

Fig 2 cFos: marker of neuronal activity

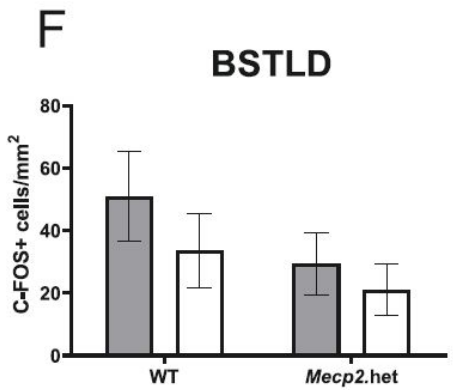


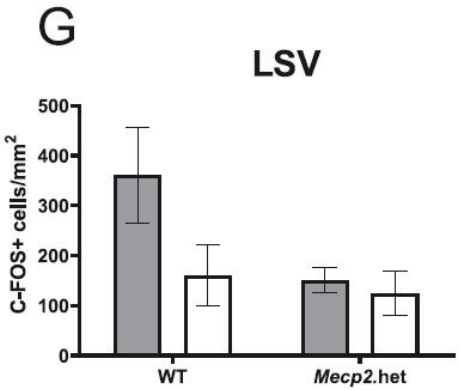
Pa: Paraventricular hypothalamic nucleus

Fig 2: Quantification



Pa: Paraventricular hypothalamic nucleus
PV: Paraventricular thalamic nucleus
BSTLD: Bed nucleus of the stria terminalis, lateral division, dorsal part
LSV: lateral septum
DG: Dentate gyrus





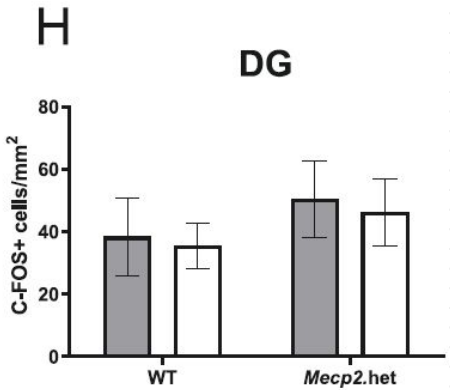


Fig 3

Paraventricular hypothalamic nucleus

CRH + cFos co-expression

AVP + cFos co-expression

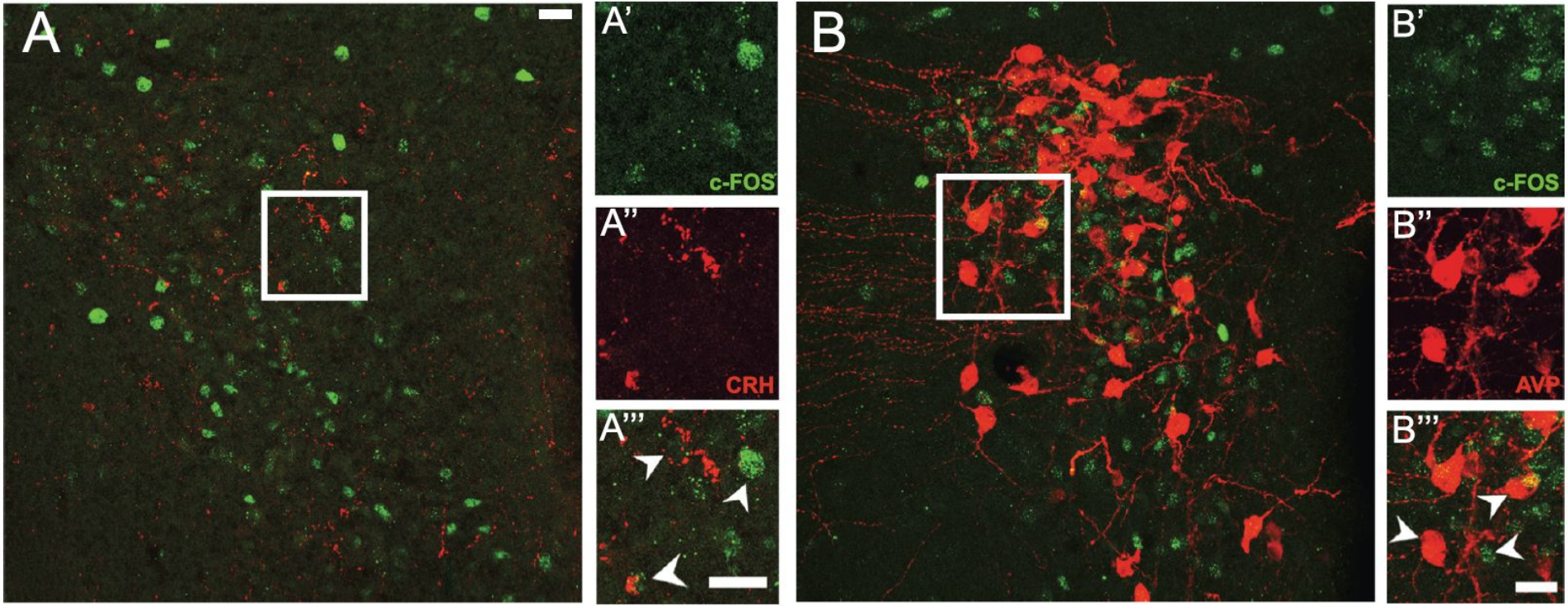
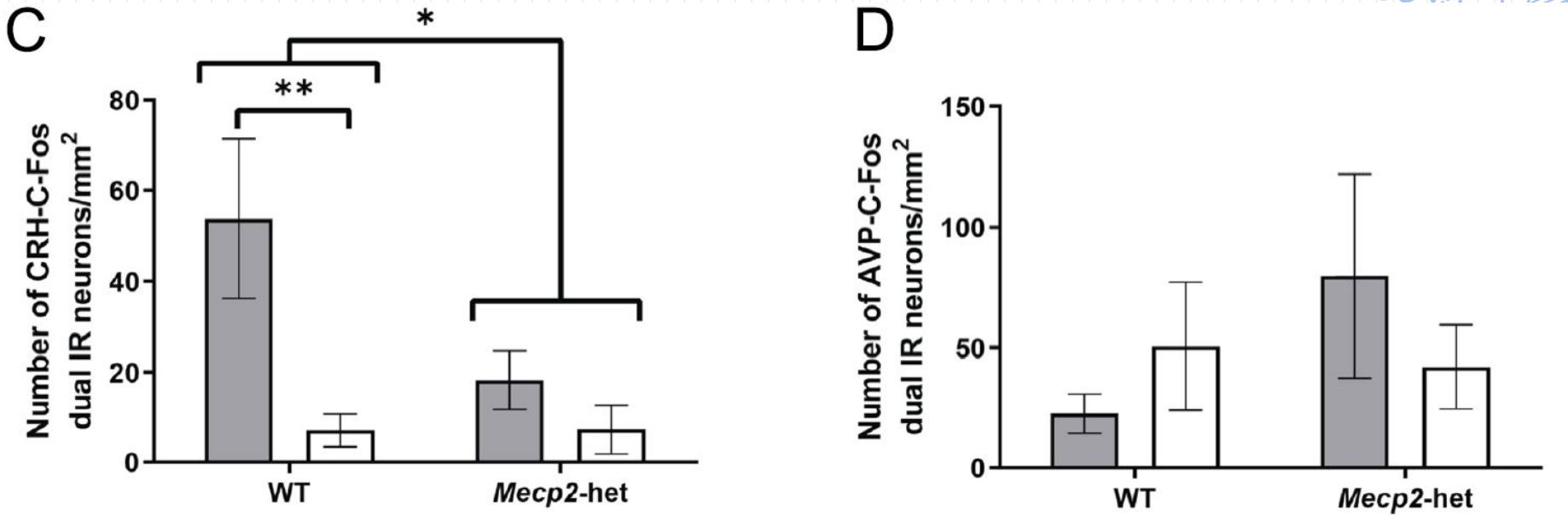


Fig 3: Quantification



Main takeaways from results

- ✘ Inverse effects of MeCP2 deficiency and ELS in mice vs humans
  - ✗ Mice: deficiency and ELS leads to reduced anxiety-like behaviors
  - ✗ Humans: deficiency and ELS lead to more vulnerability through epigenetic marks

Key Findings:

- MeCP2 deficiency and MS prevent activation of CRH neurons
  - CRH pathway is MeCP2 dependent and plays a key role in controlling neuron activity in stress-related situations
- MeCP2 is essential for proper functioning of HPA axis(hypothalamic-pituitary-adrenal axis)
  - Axis mediates effects of stressors
  - Lack of MeCP2 or ELS increase vulnerability of future psychiatric conditions b/c they interfere with axis

Conclusion + Future directions + Lingering questions

-Potential in using the CRH pathway and introduction of MeCP2 protein to treat anxiety levels in RTT patients