

co-ordinated with the Director of the Institute / Research Unit

**Institute of Developmental Genetics, Behavioural Neuroscience
Team**

PSP-Element:

G-500500-001

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Title of the highlight:

A robust and reliable non-invasive test for stress responsivity in mice

Keywords:

Mouse mutants, behaviour, acute restraint stress, corticosterone, Open Field

Central statement of the highlight in one sentence:

We developed and validated a reliable protocol to test stress responsivity in mice, which can be used in large-scale efforts to elucidate the genetic factors contributing to the development of multifactorial diseases.

Text of the highlight:

Stress is a major risk-factor in many multifactorial diseases, such as cardiovascular diseases, psychiatric disorders like anxiety and depression, as well as neurodegenerative diseases such as Alzheimer's and Parkinson's disease. Still the etiology of these diseases remains elusive, as the interplay between genetic as well as environmental factors is difficult to disentangle.

Currently mouse mutants for each single gene are generated and phenotyped in a large-scale manner by the International Mouse Phenotyping Consortium (IMPC), providing an exceptional opportunity to learn more about the genetic factors contributing to diseases. Given the importance of stress as a risk factor, it seems prudent also to include a test for stress responsivity in the phenotyping pipeline, but so far no reliable method was available.

Therefore we developed a non-invasive, robust protocol to measure stress responsivity in mice, validated it pharmacologically and demonstrated that it can be used to phenotype mouse mutants, which are all important prerequisites for methods suitable for phenotyping pipelines.

The next step is to attempt to include the stress responsivity test in the large-scale international phenotyping effort, which could greatly enhance our chances to understand the role played by stress in disease development.

Publication:

Zimprich A, Garrett L, Deussing J, Wotjak CT, Fuchs H, Gailus-Durner V, Hrabě de Angelis M, Wurst W, **Hölter SM**. A robust and reliable non-invasive test for stress responsivity in mice. Front Behav Neurosci 2014 Apr 15;8:125. doi: 10.3389/fnbeh.2014.00125. eCollection 2014

Taking account of the HMGU mission:

The highlight relates to the HMGU mission as it is a methodological development that constitutes a potentially important contribution to understanding the mechanisms of many multifactorial diseases including diabetes, cardiovascular and neuropsychiatric diseases.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:

Institute of Experimental Genetics

Acute Stress Challenge – The Method

Institute of Developmental Genetics

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Restraint Stress



20 min interval



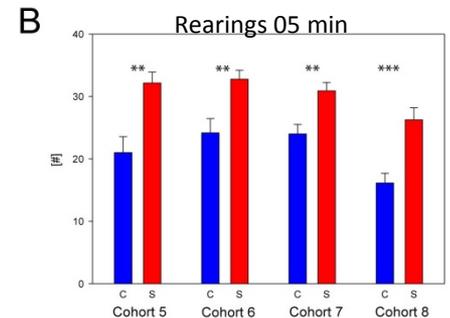
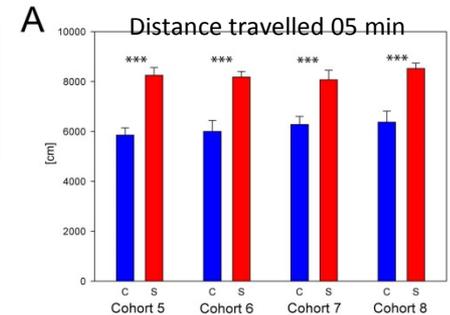
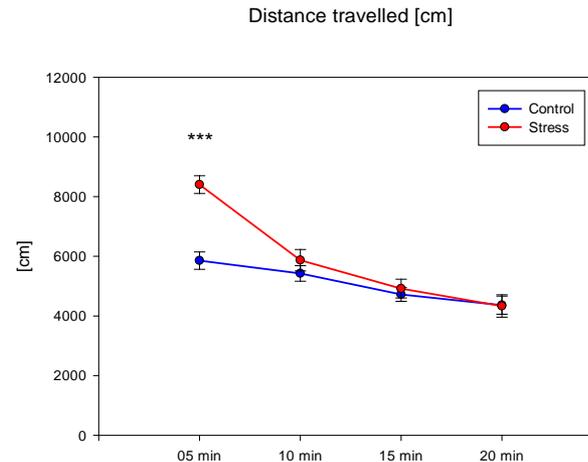
Open Field (OF)

Non-invasive stress responsivity test

Genetic mouse models can reproducibly be tested for **hyper-** and/or **hypo-**responsivity

2 h stress: **hypo**responsivity
15 min stress: **hyper**responsivity

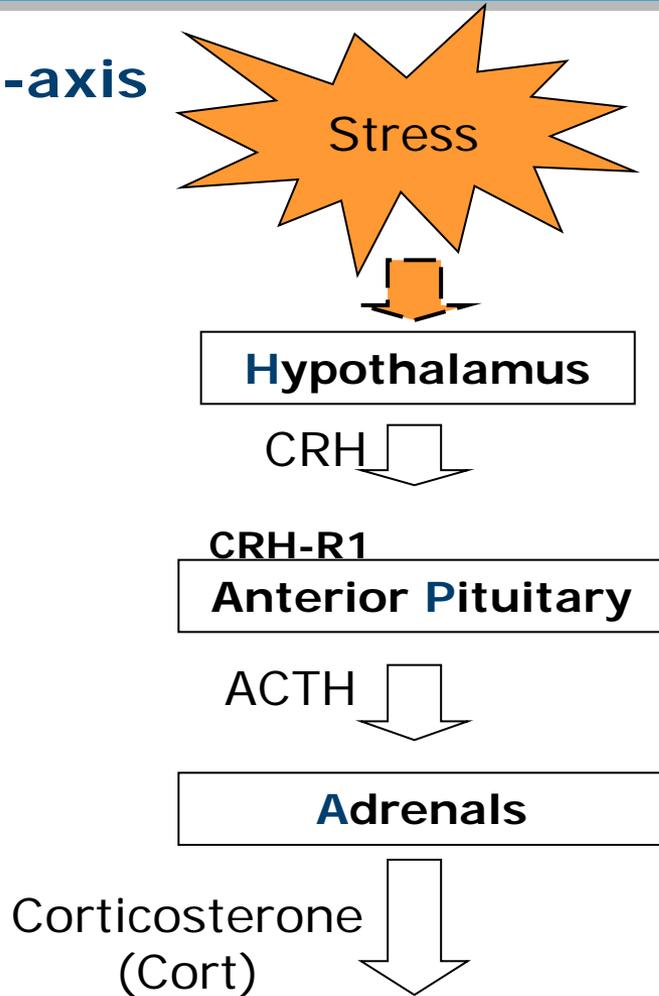
Behavioural response after stress:
Increased distance travelled and rearings
during first 5 min in OF



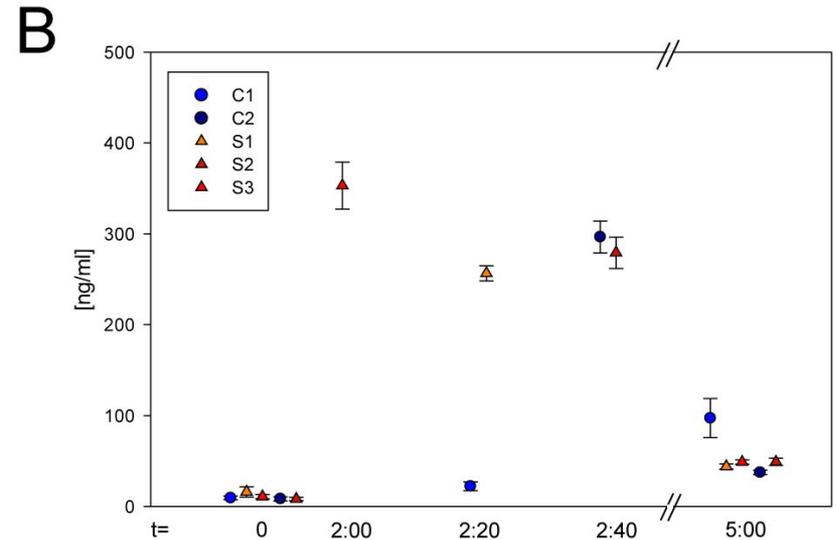
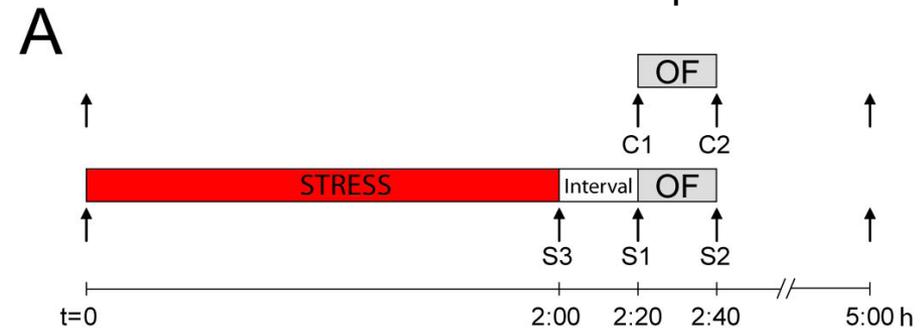
Acute Stress Challenge – Proof of Principle

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HPA-axis



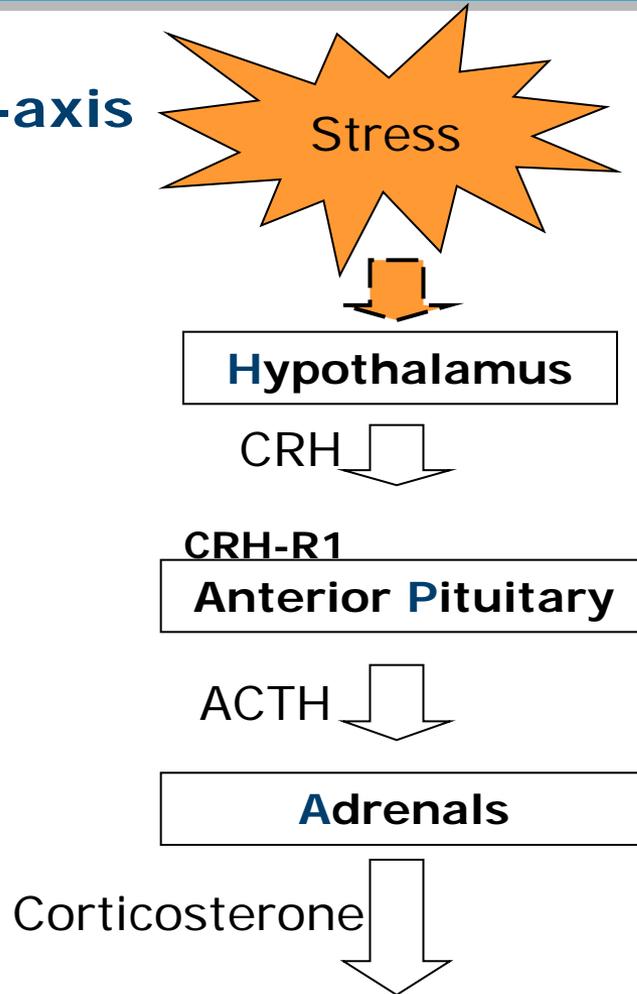
Restraint elicits Cort response



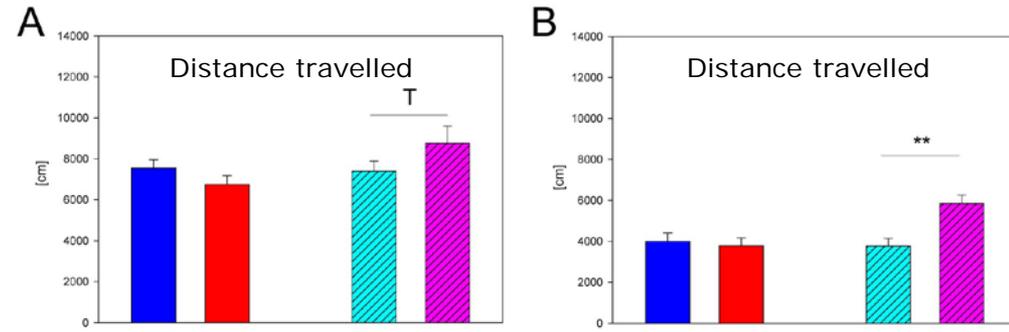
Acute Stress Challenge – Proof of Principle

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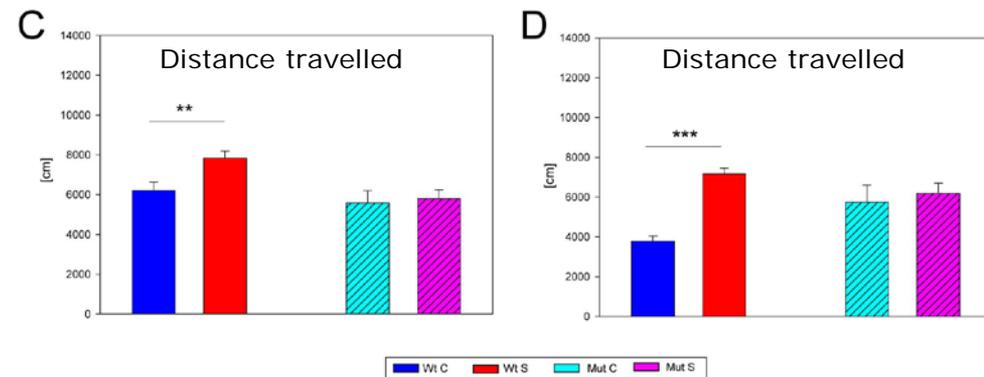
HPA-axis



CRH overexpressing mice are **hyper**-responsive



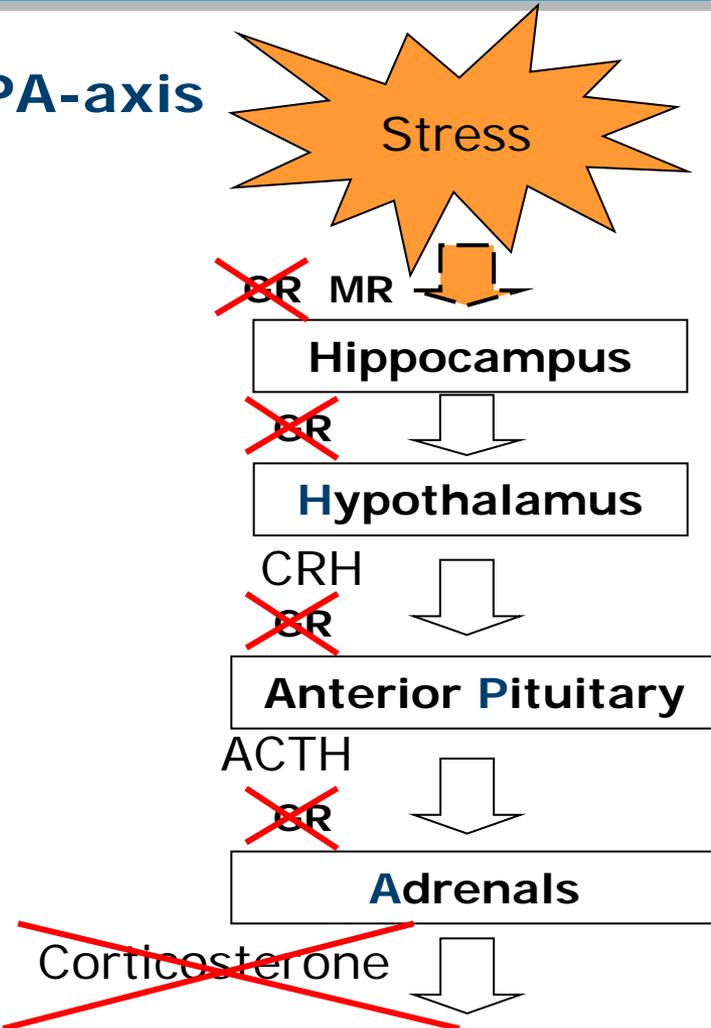
CRH-R1 ko mice are **hypo**-responsive



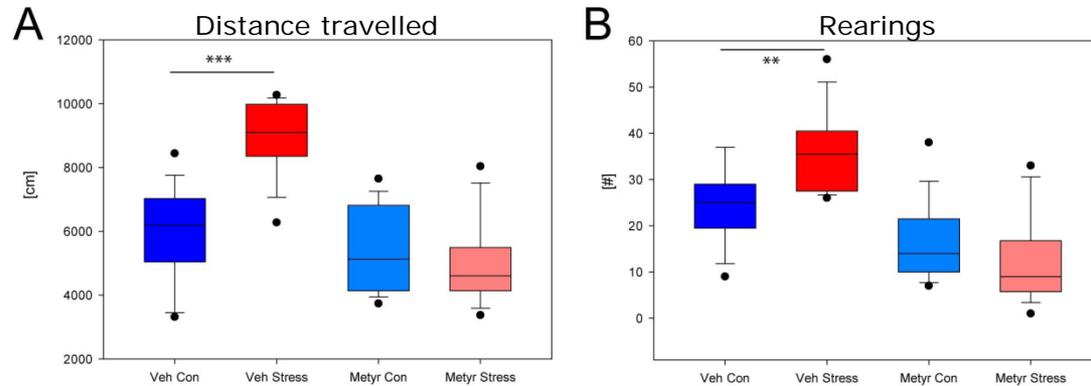
Acute Stress Challenge – Pharmacological validation

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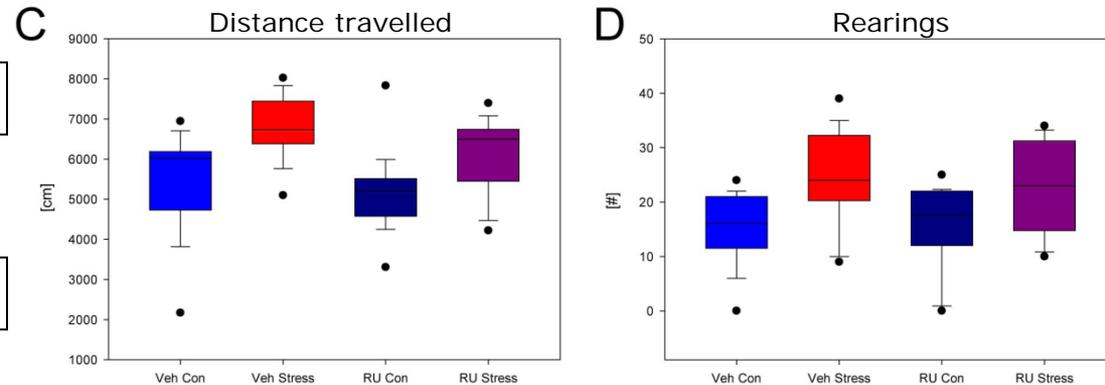
HPA-axis



Cort antagonist blocks behavioural response



GR antagonist has no effect on responsivity



Prerequisites for the robustness of our protocol:

- The Open Field is necessary as test apparatus (instead of Elevated Plus-Maze or Light/Dark Box)
- 2h restraint stress produce more reliable results than 50 or 15 min
- The 20 min interval, in which the animals are grooming, is necessary

Scope of robustness:

- Works in different Open Field Systems (ActiMot vs EthoVision)
- Works repeatedly in the same animals (no habituation or conditioning)
- Works in male and female mice
- Works in different mouse strains (C57BL/6J and N, BALB/c, C3H/HeN, but not 129S2/SvPas)
- Works with bigger restraint tubes for bigger animals
- Works at all ages