

# Schizophrenia endophenotypes and stress hyper-reactivity co-precipitate following adverse life events in genetically susceptible rats.

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## Introduction

- Schizophrenia is a mental disorder, with complex symptomatology, driven by genetic and environmental risk factors.
- The purpose of this study in rodents was to test the "three-hit hypothesis" of schizophrenia by examining the interaction between predisposing genes, early-life experience, and later-life environment.

## Approach

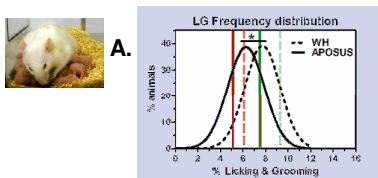
① **Genetic predisposition (G):** We have used rats of the pharmaco-genetically selected apomorphine susceptible line (APOSUS), which are characterized by schizophrenia-like phenotypes. These animals display enhanced dopamine receptor reactivity and show resistance to glucocorticoids (i.e. corticosterone; CORT). Wistar Hannover (WH) rats were used as controls.

② **Early-life experience (EE):** Poor mother-pup interaction (i.e. % licking & grooming) was used as a marker of an adverse early-life experience causing epigenetically programmed enhanced stress responsiveness.

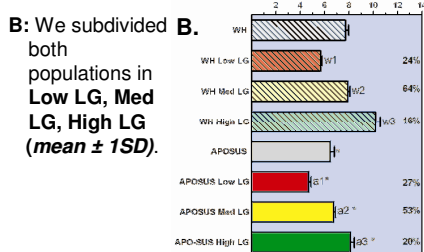
③ **Later-life environment (LE):** Isolation rearing starting from adolescence was used as unfavourable environment for late brain maturation, a condition known to produce sensorimotor gating deficits.

**Adult phenotypes.** Rats were tested on: conditioned emotional response (CER) for stress reactivity, pre-pulse inhibition (PPI) of the acoustic startle for sensorimotor gating, apomorphine-induced gnawing for dopamine sensitivity, & T-maze spontaneous alternation for working memory.

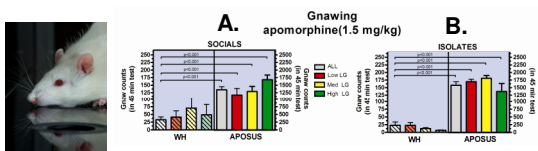
## Maternal behaviour (%LG)



A: In both rat strains, the frequency of maternal Licking & Grooming (%LG) was normally distributed across dams, but the mean of the APOSUS strain was lower.



## Dopaminergic sensitivity: G



➤ A&B: Gnawing was enhanced in the APOSUS animals no matter the maternal care history and the post-weaning rearing condition.

## Hypothesis

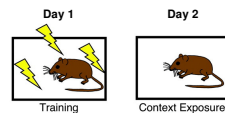
We test if, in genetically predisposed rats, neuroendocrine programming of the stress system by adverse early-life experience and later psycho-social stressors is necessary for precipitation of schizophrenia endophenotypes.

## Conclusions

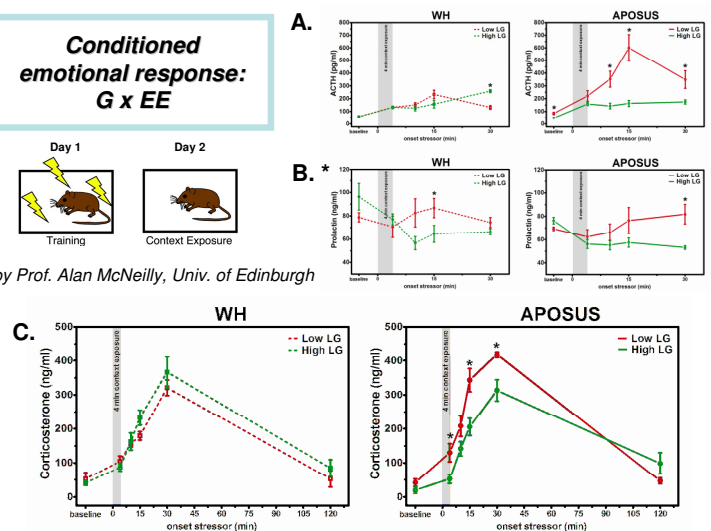
✓ Our data support the three-hit hypothesis of psychopathology: early-life adversity enhances vulnerability of the genetically predisposed APOSUS animals to a later psycho-social stressor resulting in a severe schizophrenia-like phenotype, provided central and peripheral stress reactivity is enhanced by stressful life events in the face of glucocorticoid feedback resistance.

✓ It is expected therefore that the analysis of aberrant glucocorticoid responsive genes in this model will reveal a novel susceptibility pathway and hence deliver possible novel targets for therapeutic intervention.

## Conditioned emotional response: G x EE

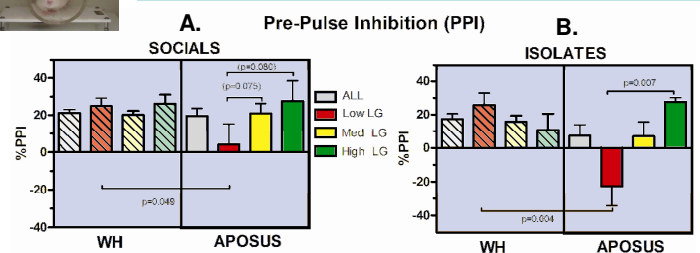


\* by Prof. Alan McNeilly, Univ. of Edinburgh



➤ ACTH [A], Prolactin [B] & CORT [C]: APOSUS Low LG display enhanced stress reactivity. However, the increase of ACTH is more robust than the one of CORT → (adrenal) hypo-responsiveness and CORT feedback resistance.

## Sensorimotor gating: G x EE x LE



➤ WISTAR (A&B):

Low LG(-) + Isolation rearing(-) = normal PPI (2 "negative" environmental life events → "positive outcome"; match)

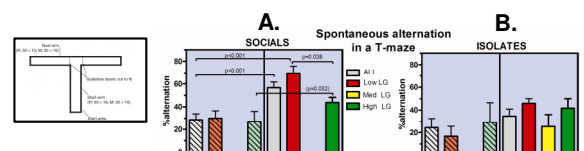
High LG(+) + Isolation rearing(-) = PPI deficit (1 "positive" + 1 "negative" environmental life event → "negative outcome"; mismatch)

➤ APOSUS (A&B):

Increased early life adversity (Low LG) leads to a PPI impairment (2 hits).

PPI is further reduced by isolation rearing (3 hits).

## Working memory: G x EE x LE



➤ A&B: Socially reared APOSUS rats display enhanced working memory; especially those with low maternal care history. Isolation rearing abolished those effects adding a working memory deficit to the APOSUS phenotype.