Blood glucose and insulin levels following an oral glucose challenge are promising biomarkers in the zQ175 knock-in mouse model of Huntington's disease

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BACKGROUND

Glucose homeostasis is maintained as a closed feedback loop involving the pancreatic islet cells, liver, brain and peripheral tissues, including muscles and adipose tissue. The modes of communication between **peripheral organs and the brain** are complex and still being revealed, and also glucose regulation mechanisms independent of CNS activity have been postulated (Fulgenzi *et al.,* 2020).

Dysfunction of the **hypothalamus**, the brain part that controls energy balance by integrating both central and peripheral signals, has been demonstrated to be at least partly responsible for the metabolic alterations seen in **Huntington's disease** mouse models and patients (Hult *et al.,* 2011).

Besides, **peripheral interference** of mutant huntingtin with insulin signalling has been postulated as an underlying mechanism of increased energy expenditure seen in Huntington patients, which may become clinically relevant in carriers of large CAG repeat sizes (Aziz *et al.,* 2010).

Aim

We set out to explore the potential of metabolic parameters as biomarkers and surrogate endpoints for assessing the efficacy of experimental Huntington's disease (HD) therapies in the zQ175 mutant Huntingtin knock-in mouse model (zQ175 Htt KI mice).

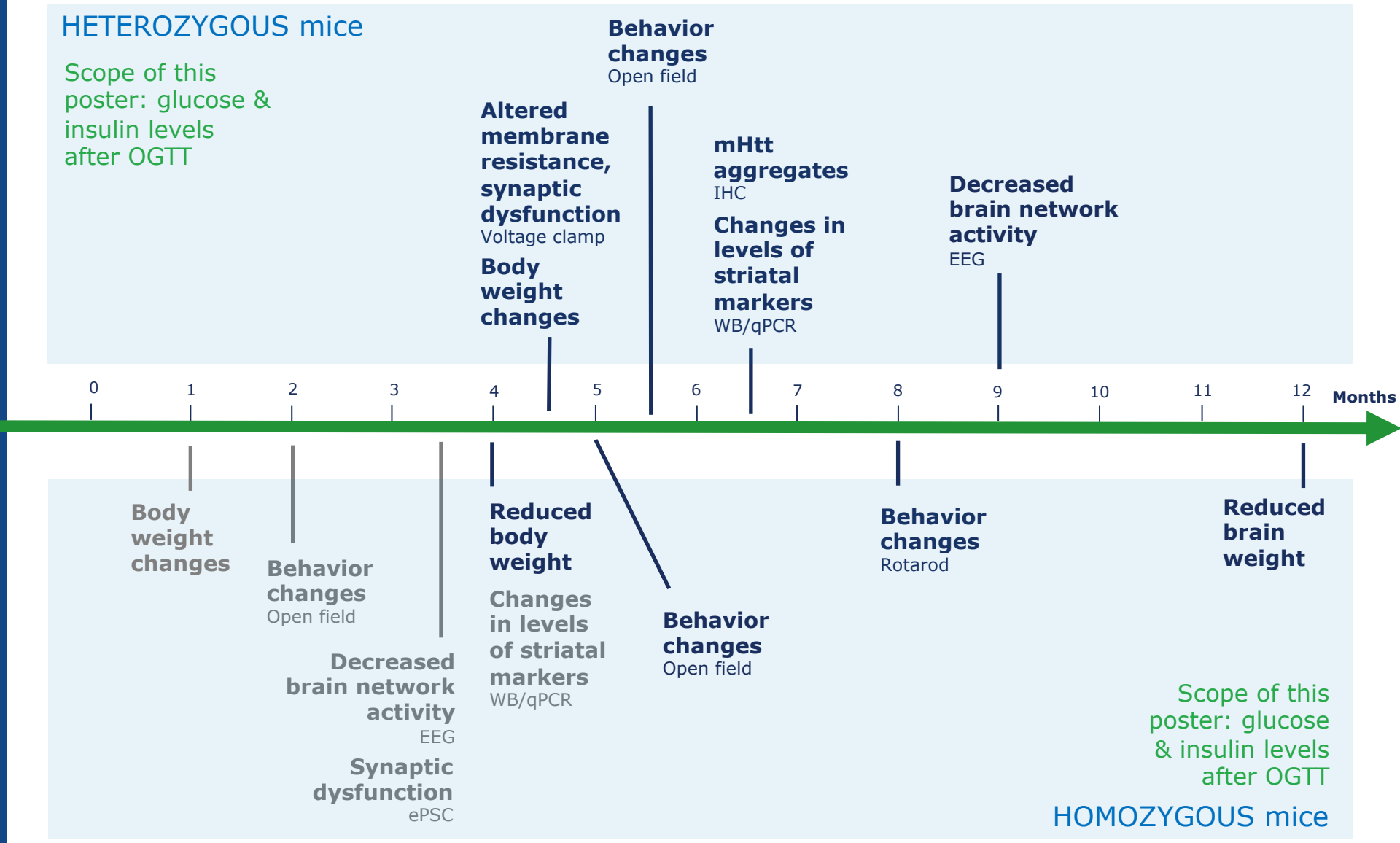
Method

We subjected these mice to an oral glucose tolerance test (OGTT), entailing the measurement of blood glucose levels and insulin secretion levels at different time-points post oral glucose administration.

The zQ175 Htt KI model for Huntington's disease faithfully recapitulates many of the clinical phenotypes in the absence of overexpression artefacts

- C57BL/6J background
- The zQ175 knock-in allele has the mouse *Htt* exon 1 replaced by the human *HTT* exon 1 sequence with a ~180 CAG repeat tract
- Endogenous expression driven by the mouse *Htt* promotor, hence towards many of the body's tissues, with the highest levels of activity in the brain
- Age of onset of pathological changes and functional deficits, both in heterozygous and homozygous zQ175 Htt KI mice, is illustrated on the timeline below

Pathological changes and functional deficits in heterozygous and homozygous zQ175 Htt KI mice



Blue: in-house data.
Grey: literature data

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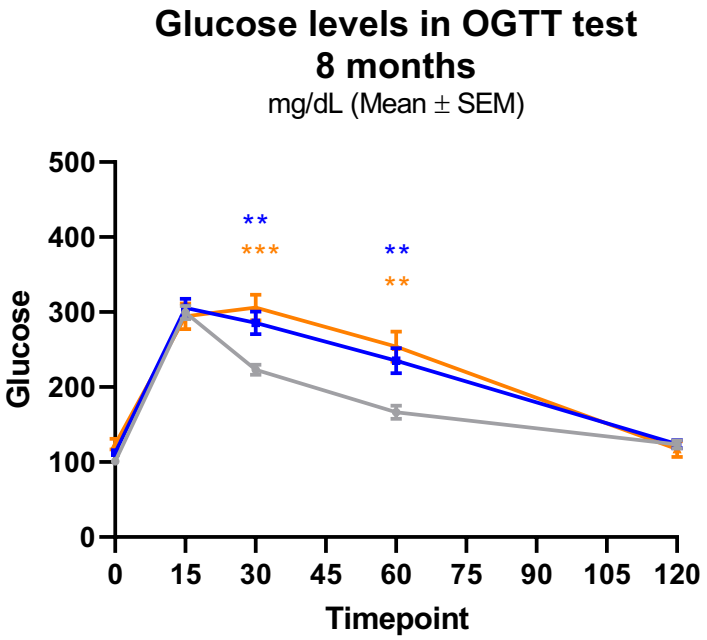
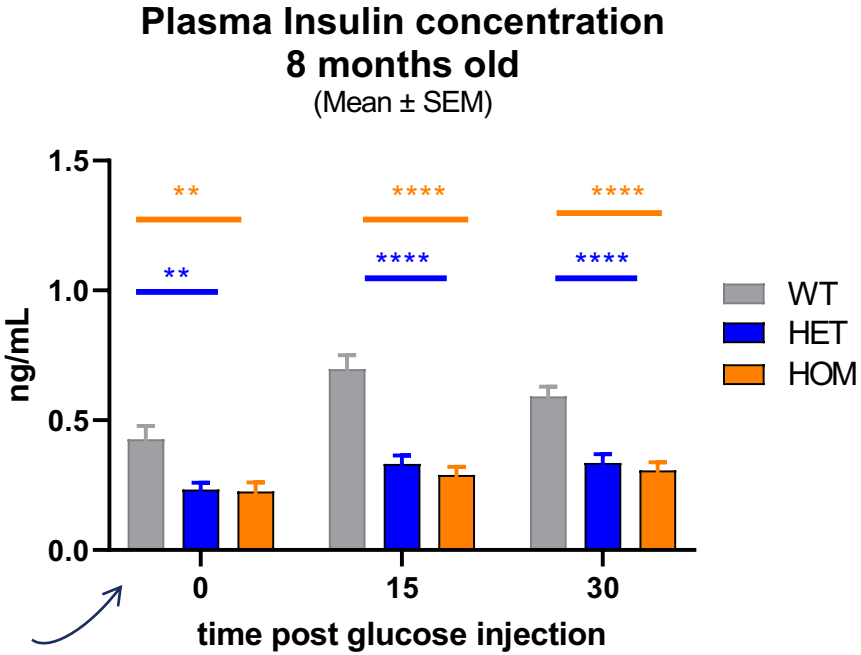
zQ175 Htt KI mice show significant glucose dyshomeostasis and low insulin levels after an oral glucose challenge

Oral glucose tolerance test (OGTT, 1g/kg glucose, administered PO after a 5-6h fasting period); plasma glucose levels (measured via glucometer) and insulin levels (measured via ELISA)

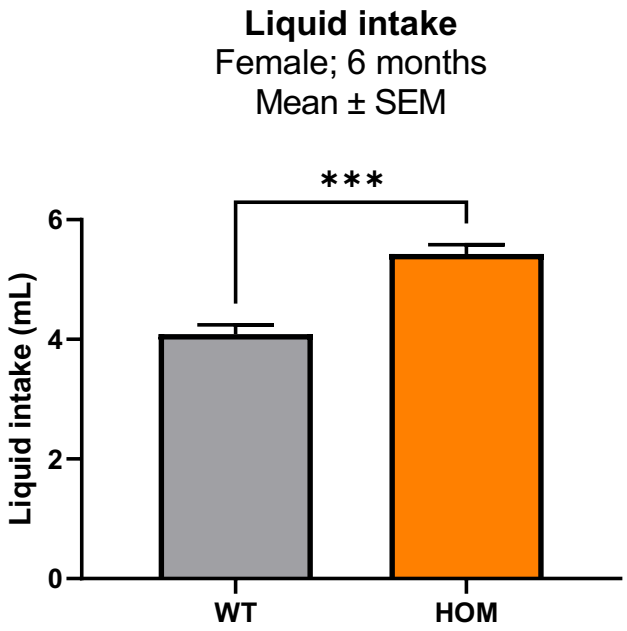


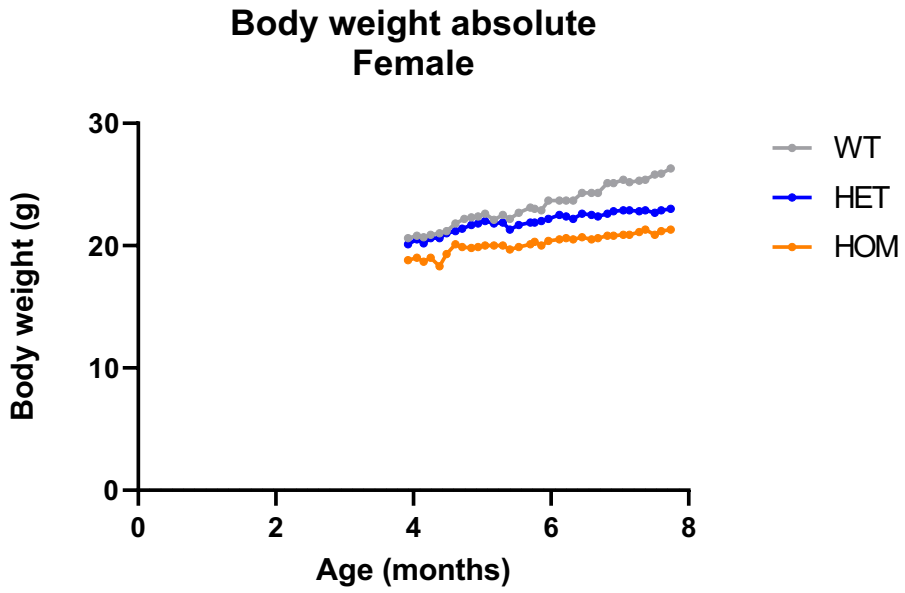


Basal insulin deficit is currently being investigated further

Group sizes are 15WT/15HET/15HOM, 8-months old mice, all females. Statistics: 2way ANOVA-multiple comparisons

Deregulation of glucose homeostasis in zQ175 Htt KI mice is also manifested in their aberrant drinking behaviour and reduced body weights



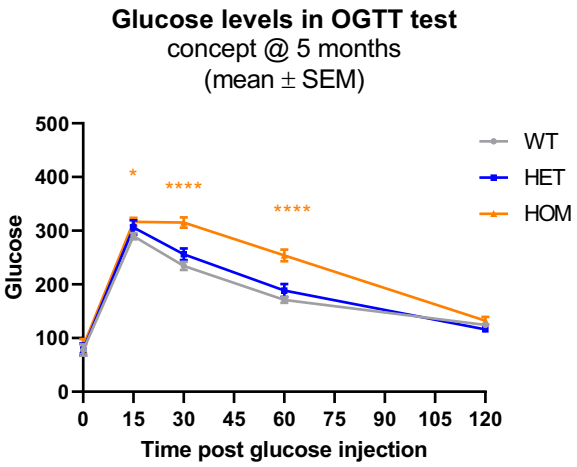


Group sizes are 15WT/15HET/15HOM, all females. Statistics: 2way ANOVA-multiple comparisons

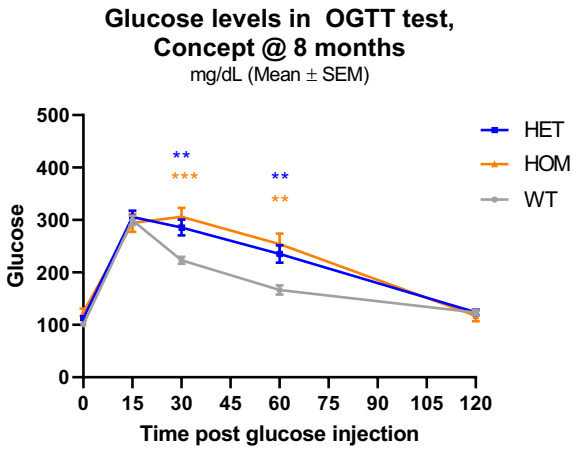
The glucose dyshomeostasis phenotype in OGTT seems to set on earlier in homozygous compared to heterozygous mice

Oral glucose tolerance test (OGTT, 1g/kg glucose, administered PO after a 5-6h fasting period); plasma glucose levels (measured via glucometer)

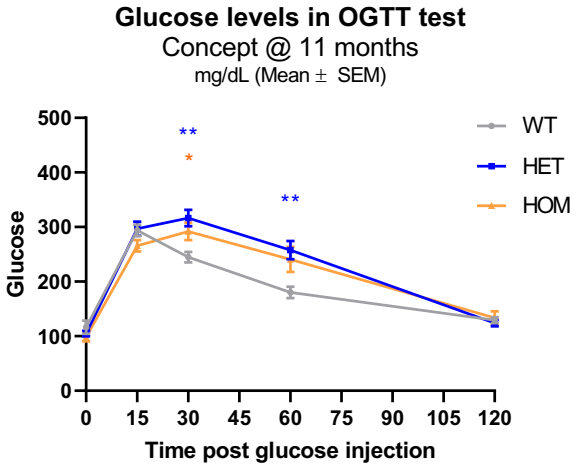
5 months



8 months



11 months

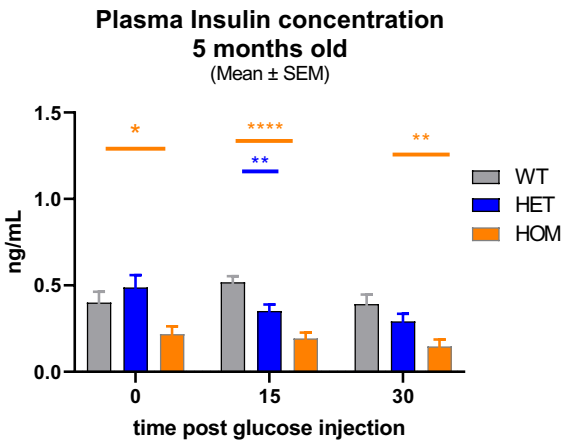


Group sizes are 15WT/15HET/15HOM, all females. Statistics: 2way ANOVA-multiple comparisons

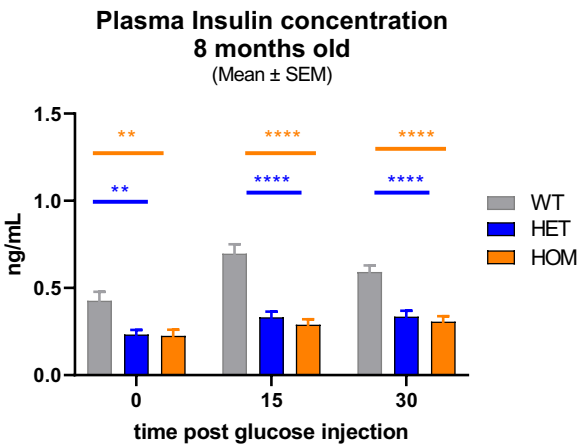
The low insulin levels phenotype in OGTT seems to set on earlier in homozygous compared to heterozygous mice

Oral glucose tolerance test (OGTT, 1g/kg glucose, administered PO after a 5-6h fasting period); plasma insulin levels (measured via ELISA); insulin secretion/production assessments in pancreas are planned to explain basal insulin deficits

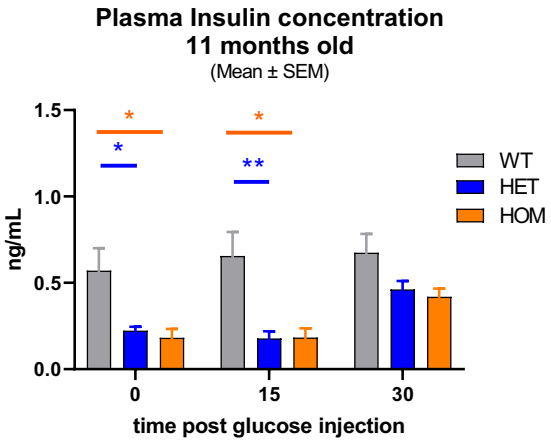
5 months



8 months

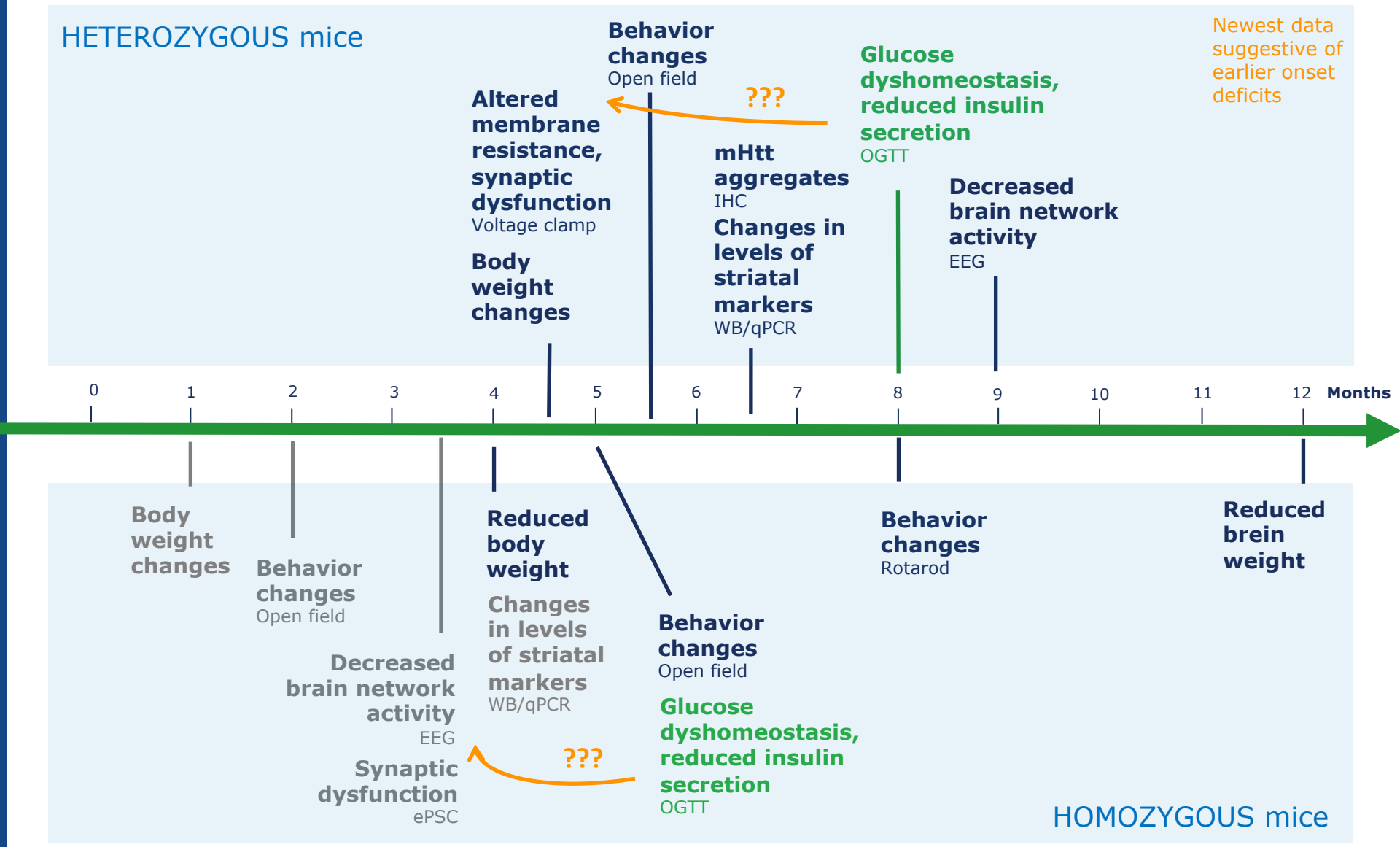


11 months



Group sizes are 15WT/15HET/15HOM, all females. Statistics: 2way ANOVA- multiple comparisons; 2 outliers removed from 5months with Grubbs's test

Pathological changes and functional deficits in heterozygous and homozygous zQ175 Htt KI mice



Next steps

- Further investigation if the metabolic parameters investigated can serve as an early marker of **disease onset** and/or **disease progression** in the zQ175 Htt KI model

- Further confirmation of preliminary results that metabolic parameters can serve as powerful **readouts to assess therapies** aimed at alleviating cellular toxicity by mutant Huntingtin

- Gain further insights in the **mechanisms** driving the observed glucose dyshomeostasis in zQ175 Htt KI mice, in which mutant *HTT* expression hence toxicity, is driven both to the brain and peripheral tissue

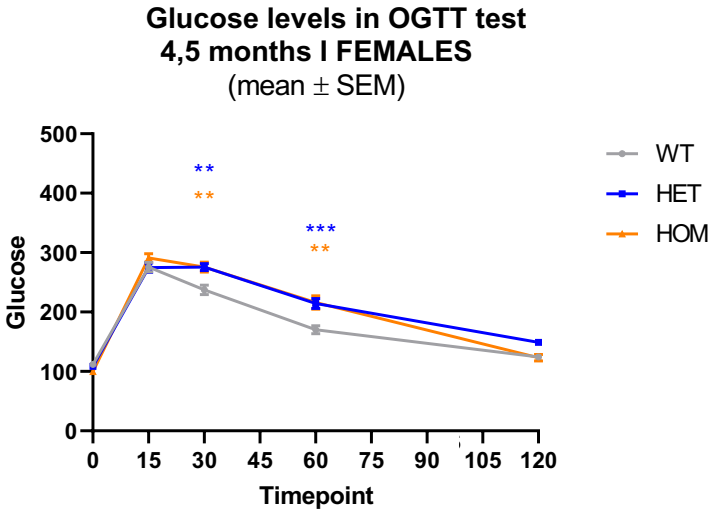
  -> preliminary data in the following slides

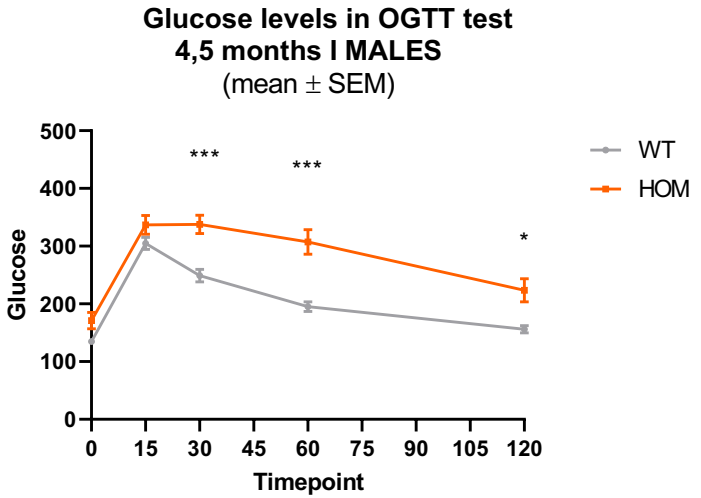
- **Other biomarkers** currently being investigated in heterozygous and homozygous zQ175 Htt KI mice at reMYND include the following: EEG, NF-L, 8-OH-dG, 18S-OH-cholesterol, BDNF

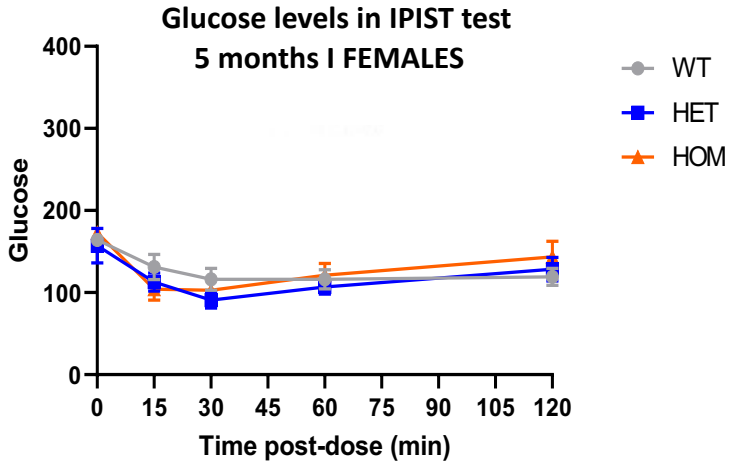
-> don't hesitate to reach out for more information

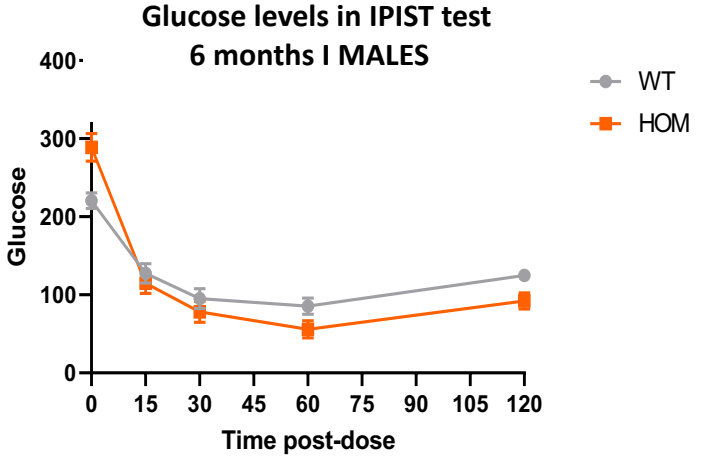
Insulin resistance does not seem a key mechanism behind the observed glucose dyshomeostasis phenotype

Intraperitoneal insulin sensitivity test (IPIST) in 4,5- and 6-months-old zQ175 Htt KI mice: 0,75U/kg insulin, mice not fasted
Insulin secretion/production assessments in pancreas are planned





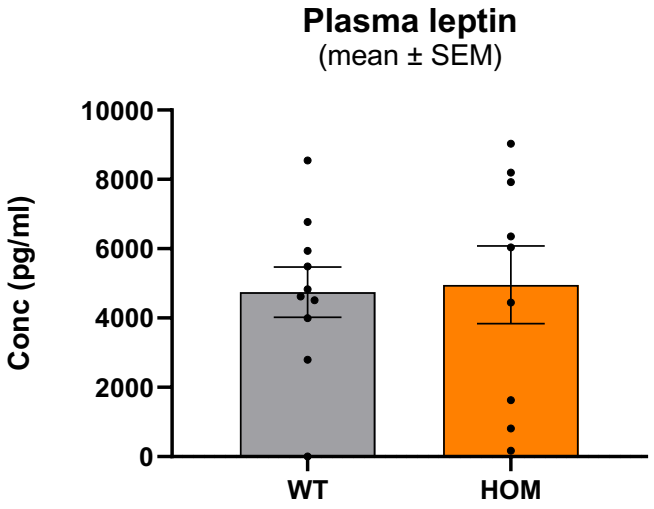


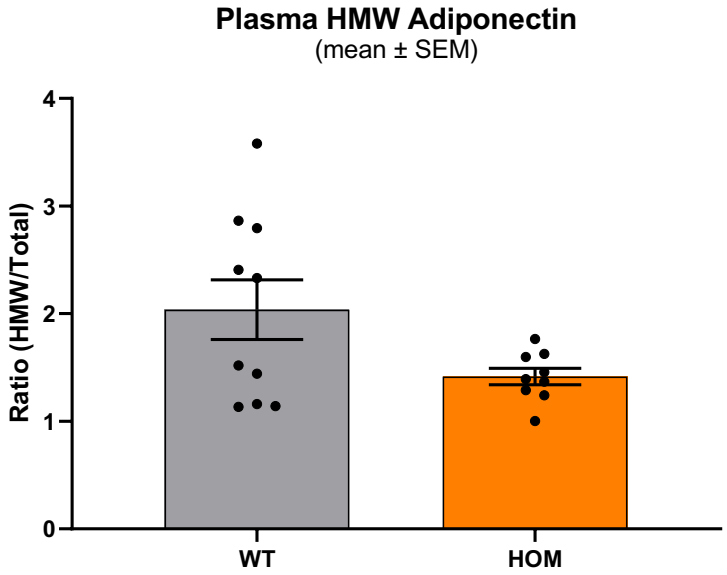


Group sizes are 8WT/8HET/8HOM. Statistics: 2way ANOVA-multiple comparisons

Adipocyte tissue might be affected and contribute to the observed glucose dyshomeostasis phenotype

Plasma leptin and HMW adiponectin levels in 12-months-old zQ175 Htt KI mice via ELISA, preliminary data





Rationale: Adipocytes have been postulated to be affected in Huntington's disease. Impaired concentrations of the adipokine hormones leptin and adiponectin might contribute to the weight loss observed both in patients and HD animal models.

Group sizes are 10WT/10HOM, all females. Statistics: 2way ANOVA

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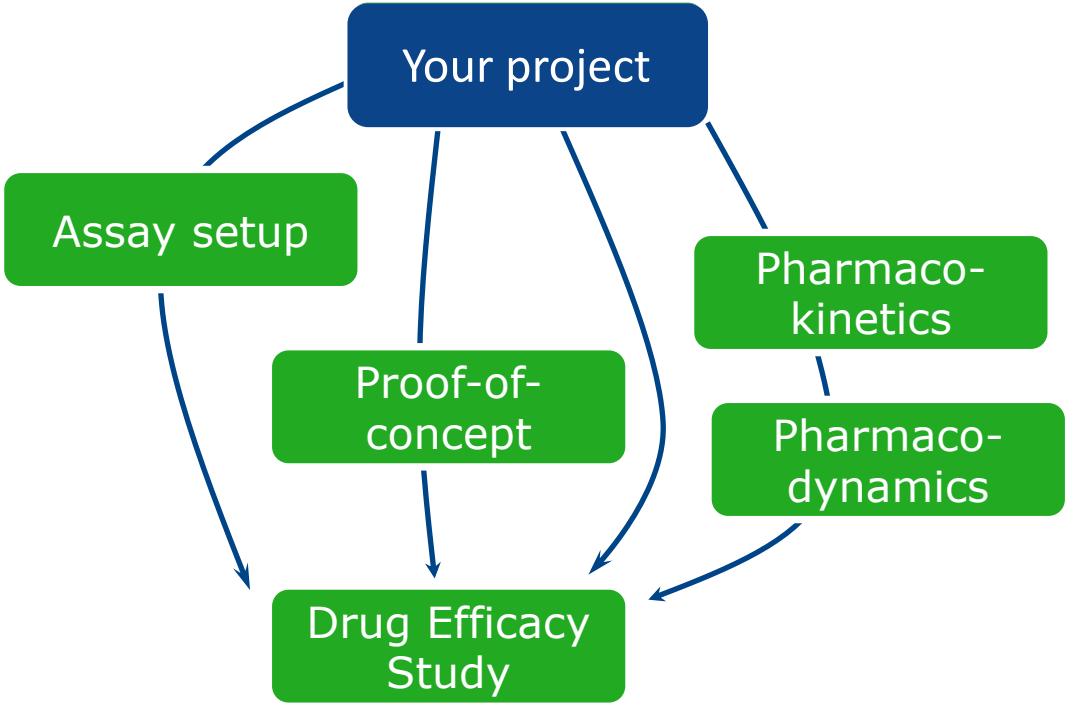

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