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Gene-environment interactions modulating cognitive and affective endophenotypes in mice

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Disorders with high genetic loads (e.g. HD) Disorders with complex polygenic & environmental loads (e.g. schizophrenia, depression, autism, dementia)

Disorders with high environmental loads (e.g. stroke)



GENETIC FACTORS monogenic polygenic (Genome)



ENVIRONMENTAL FACTORS mental/physical activity stressors, toxins, diet... ('Envirome')



Tandem repeat polymorphisms and mutations



Huntington's Disease

- Fatal neurodegenerative disorder with autosomal dominant inheritance
- Psychiatric symptoms (e.g. depression), cognitive deficits (culminating in dementia), and a movement disorder (e.g. chorea)
- Caused by a CAG/glutamine repeat expansion in huntingtin (HD Collab. Research Group, 1993, Cell) which is most toxic to specific neuronal populations in the cerebral cortex and striatum (Wang et al., 2014, Nature Med.)





Transgenic HD mice

- R6/1 mice expressing human exon 1 transgene encoding expanded polyglutamine in the huntingtin N-terminal fragment (Mangiarini et al., 1996, Cell)
- Progressive neurodegenerative phenotype, including affective, cognitive and motor deficits







Somatosensory discrimination learning test





Mazarakis et al., 2005, J. Neurosci.

Motor presymptomatic HD mice have a deficit in somatosensory discrimination learning



Trials

Mazarakis et al., 2005, J. Neurosci.



Motor presymptomatic HD mice have a deficit in experience-dependent barrel cortex plasticity



Mazarakis et al., 2005, J. Neurosci.

Spatial learning and memory in the Morris water maze

- Spatial navigation task
- •Repeated daily trials to locate platform
- •Probe trial: no platform present





Frequency, duration and latency to the quadrant and platform can be used as measures of memory acquisition A GSK-3β signaling abnormality in the cerebral cortex of HD mice correlates with cognitive deficits



Molecular and cellular mediators of cognitive deficits



HD mice develop a sexually dimorphic depression-like behavioural endophenotype by 12 weeks of age

Novelty suppressed feeding test (NSFT)

Antidepressants with clinical efficacy rescue this behavioural sign





Pang et al., 2009, Hum. Mol. Genet.

Depression-like behaviour in female HD mice is rescued by chronic administration of an SSRI

Sacharin-preference test (SPT) of anhedonia





Disease onset and progression in the R6/1 transgenic mouse model of HD



Environmental enrichment enhances activity levels



Nithianantharajah & Hannan, 2006, Nature Rev. Neurosci.

Environmental enrichment delays disease onset



Subsequent studies exploring environmental enrichment, cognitive and/or motor stimulation in HD mice: Hockly et al., 2002 ('minimal enrichment'); Spires et al., 2004; Schilling et al., 2004; Lazic et al., 2006; Pang et al., 2006, 2009; Kohl et al., 2007; van Dellen et al., 2008; Nithianantharajah et al., 2008; Benn et al., 2010; Zajac et al., 2010; Renoir et al., 2011; Wood et al., 2011; Du et al., 2012 Evidence for environmental modifiers in clinical HD

 Wexler et al.; US-Venezuela Collaborative Research Project, 2004, PNAS

- Analysis of large Venezuelan kindreds showing that the remaining variance not explained by CAG repeat length has a major environmental component

• Trembath et al., Delatycki, 2010, Mov. Disorders

- Retrospective study of Australian & New Zealand families indicating that 'passivity' (reduced activity) is a risk factor contributing to earlier age of HD onset

 Twin studies provide further evidence (although somatic CAG repeat instability and stochastic epigenetic variability may also play a role)



huntingtin gene

Hypothesised mechanisms mediating the beneficial effects of environmental enrichment

Gene expression? (experience-dependent regulation) Cellular plasticity? (neurogenesis & synaptic plasticity)



Environmental enrichment delays onset of hippocampal-dependent cognitive deficits in HD mice





Nithianantharajah et al., 2008, Neurobiol. Dis.

Barnes circular maze

A depressive-like behavioural endophenotype is rescued by environmental enrichment

Performance in the forced-swim test (FST) responds to clinically effective antidepressants



Pang et al., 2009, Hum. Mol. Genet.

Parsing the components of environmental enrichment: Can enhanced voluntary physical exercise alone induce beneficial effects?



Nithianantharajah & Hannan, 2006, Nature Rev. Neurosci.

Abnormal stress response in female HD mice is ameliorated by increased voluntary exercise



Wheeling running delays onset of cognitive, affective and motor deficits in HD mice: Pang et al., 2006; van Dellen et al., 2008; Renoir et al., 2012

Renoir et al., 2013, J. Physiol.



Assessing short-term spatial memory in the Y-maze

TRAINING TRIAL





e.g. 10 min

e.g. 5 min

Stress as a modulator of pathogenesis: Elevated stress hormone accelerates cognitive deficits



Experience-dependent HPA axis dysfunction in HD mice: Du et al., 2012, Transl. Psychiatry

Mo et al., 2014, Neurobiol. Dis.

HD

WT

PHARMACOLOGICAL **MODULATORS** (e.g. 'ENVIROMIMETICS') **MOLECULAR ENVIRONMENTAL** (\mathbf{Q}) **MODULATORS MEDIATORS** huntingtin protein ? SELECTIVE CELLULAR DYSFUNCTION $\left(CAG\right)^{n+x}$ **MOTOR, COGNITIVE & PSYCHIATRIC SYMPTOMS**

huntingtin gene

Potential mechanisms mediating brain and cognitive reserve (BCR)



Nithianantharajah & Hannan, 2009, Prog. Neurobiol.



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Gene-environment interactions and adult neurogenesis



Wheel running delays the onset of a short-term spatial memory deficit in HD transgenic mice



Running delays onset of cognitive, affective and motor deficits in HD mice: van Dellen et al., 2008; Renoir et al., 2012

Pang et al., 2006, Neuroscience