

Animal Research Review Panel, Sydney, 2nd October 2013

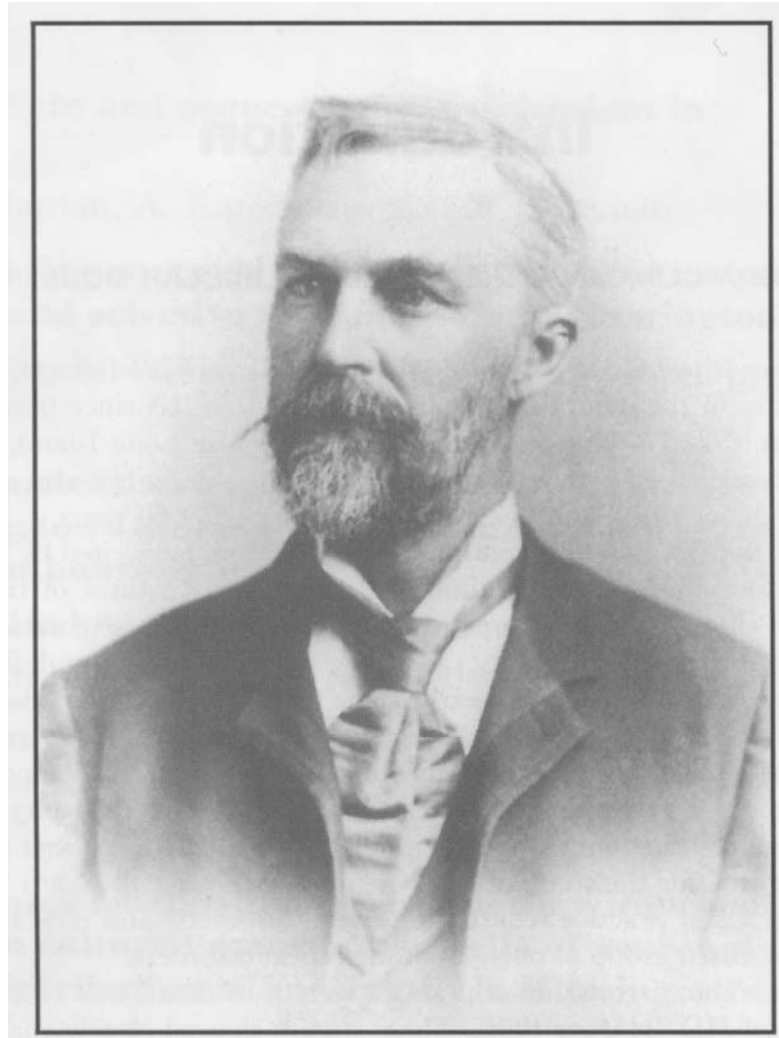
Environmental enrichment and experience-dependent plasticity in mouse models of brain disorders

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Can enhanced mental and physical activity delay the onset of brain disorders such as Alzheimer's or Huntington's disease?

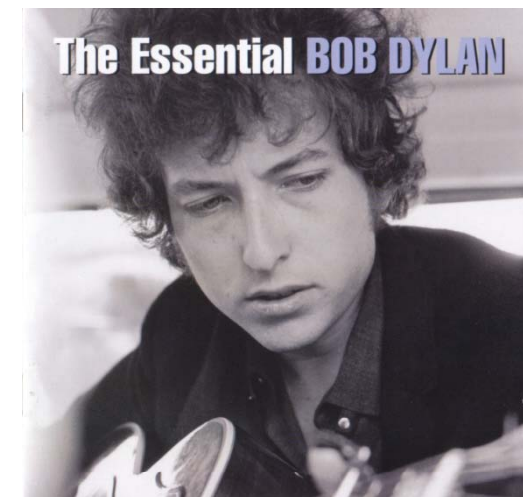
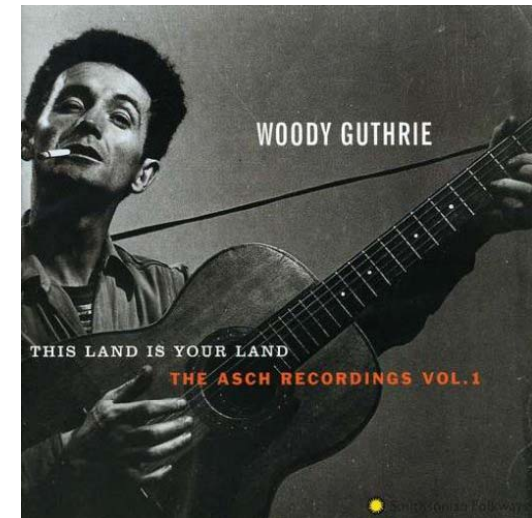


*I got this thing called chorea in my head
wanna walk but I fall down instead
folks say "Woody, he's just drunk again"
but I haven't had a drink since I don't know when
besides...I only drink when I'm alone...or with somebody.
My arms felt funny moving all the time
and sometimes my head didn't feel like mine
kept telling myself it was the Ballantine Ale
and them jugs of wine on the writing trail
I prefer a disease you can sober up from.*

“Huntington’s Chorea Blues”, **Woody Guthrie**

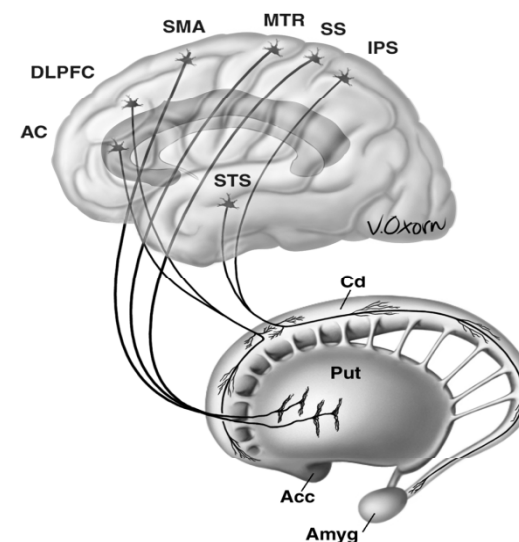
*Hey hey Woody Guthrie I wrote you a song
About a funny old world that’s a coming along
It’s sick and it’s hungry it’s tired and it’s torn
It looks like it’s dying and it’s hardly been born...*

“Song for Woody”, **Bob Dylan**

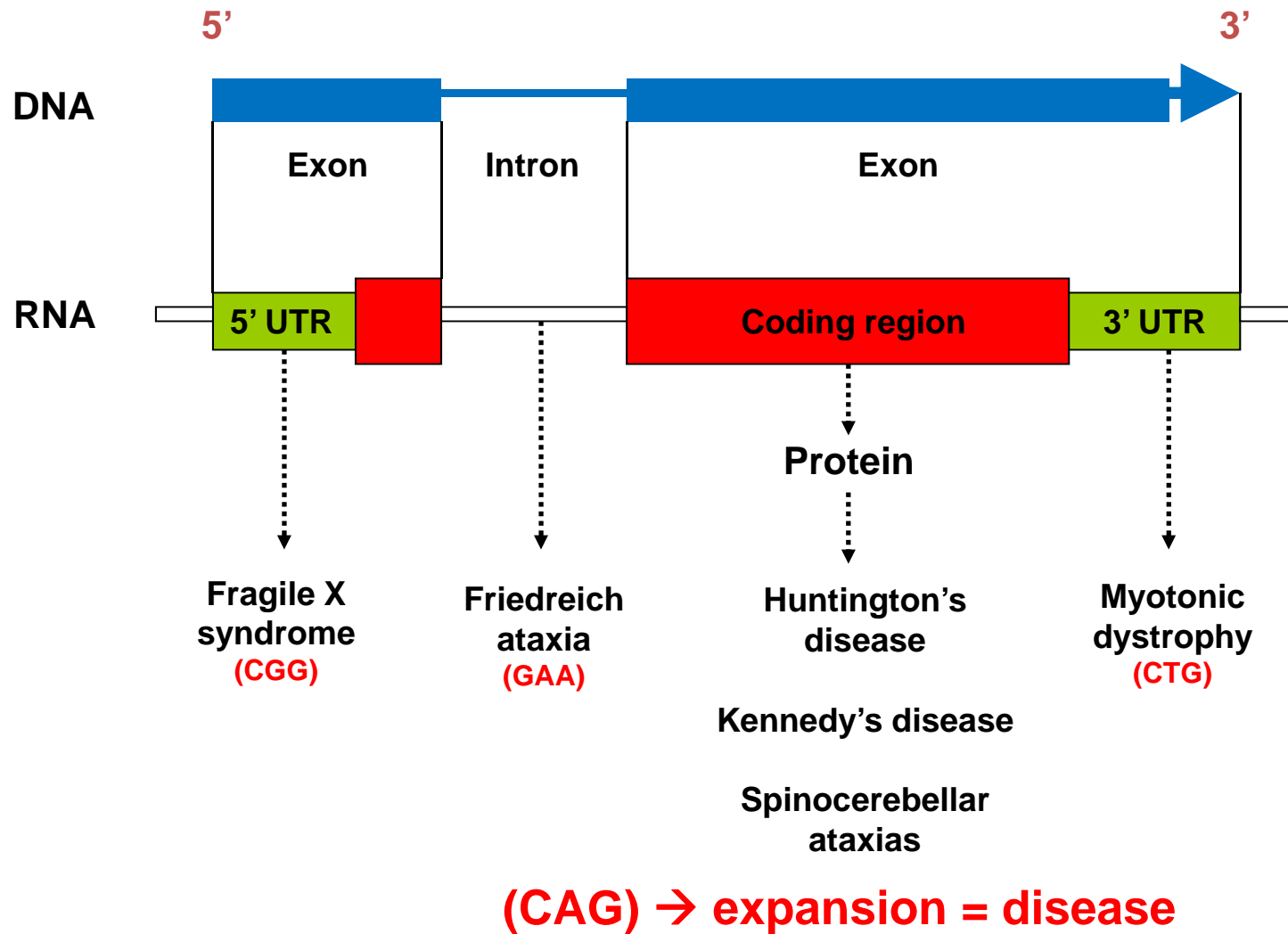


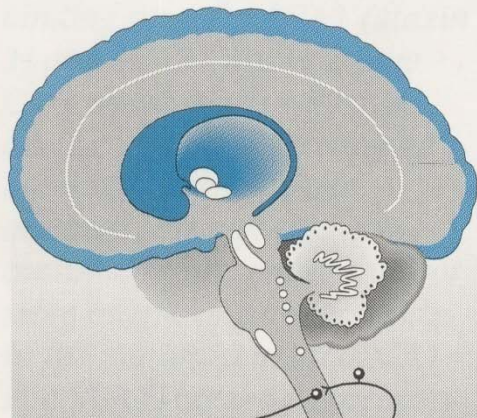
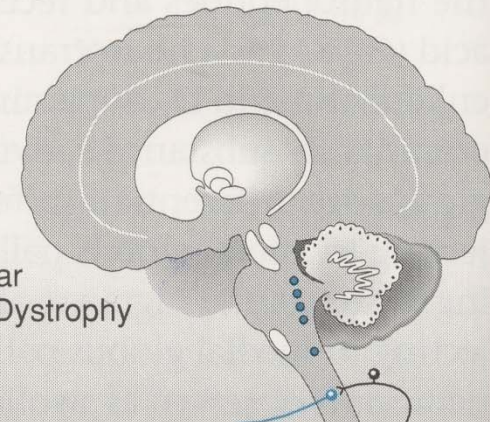
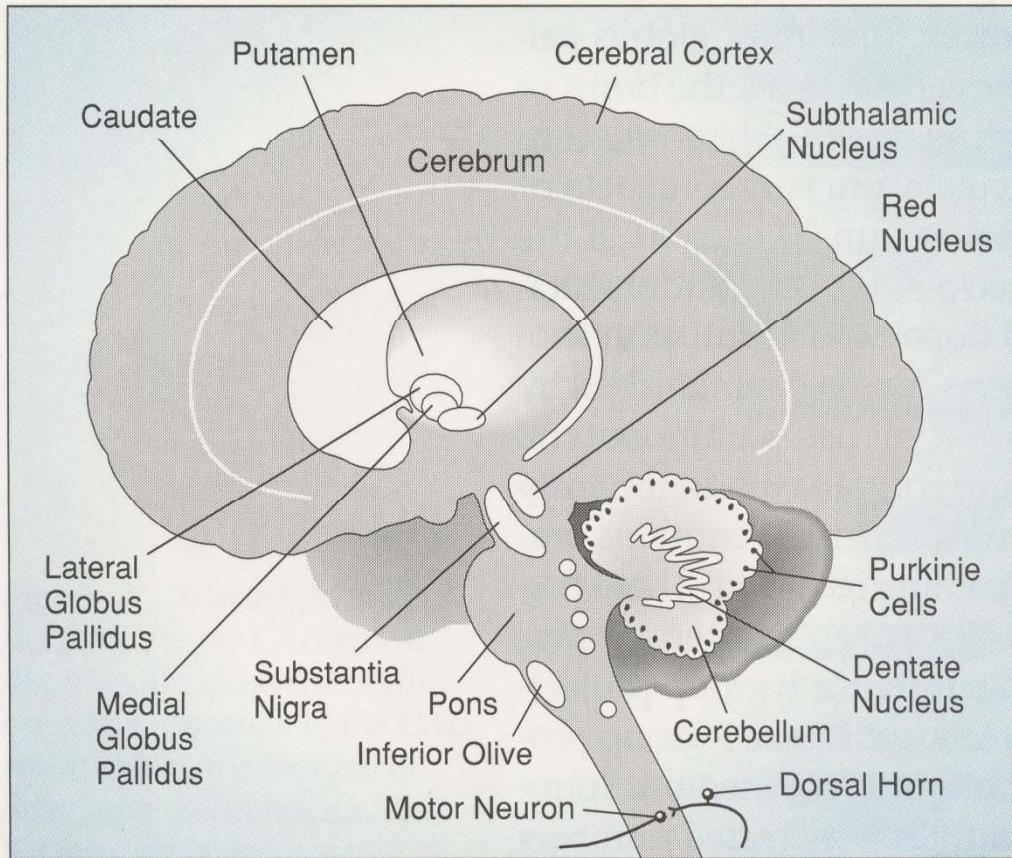
Huntington's Disease (HD)

- Fatal brain disorder caused by a gene mutation passed on to ~50% of children in HD families
- Cognitive deficits (culminating in dementia), psychiatric symptoms (e.g. depression) and a movement disorder (e.g. chorea)
- Onset usually in 4th or 5th decade of life (5% of cases have juvenile onset)



Huntington's disease is caused by a 'genetic stutter'

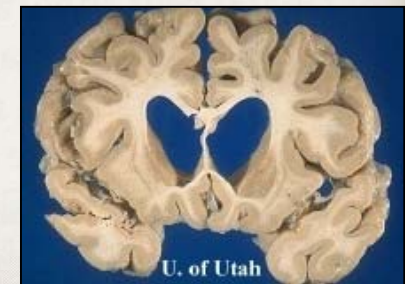
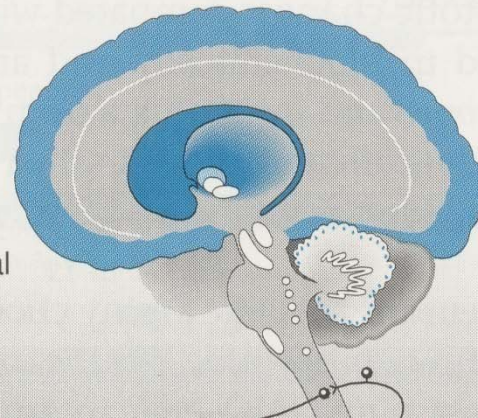




Huntington's Disease

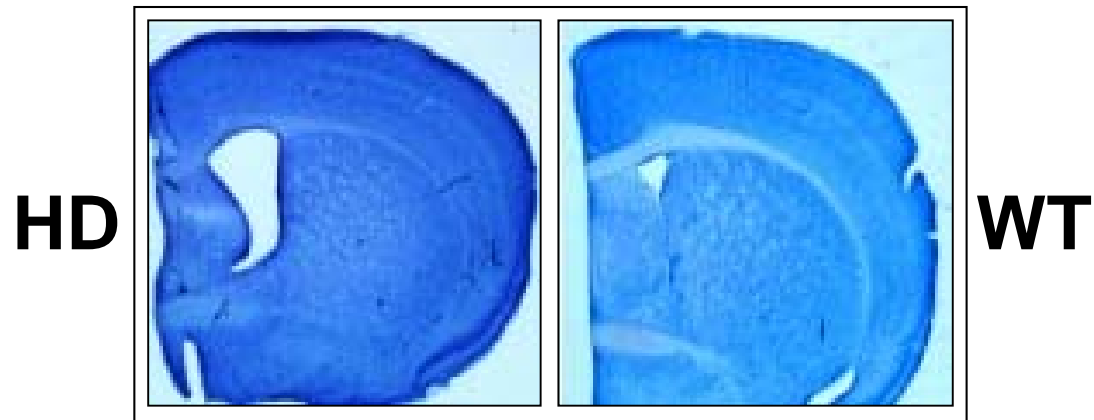
Minimal

Maximal

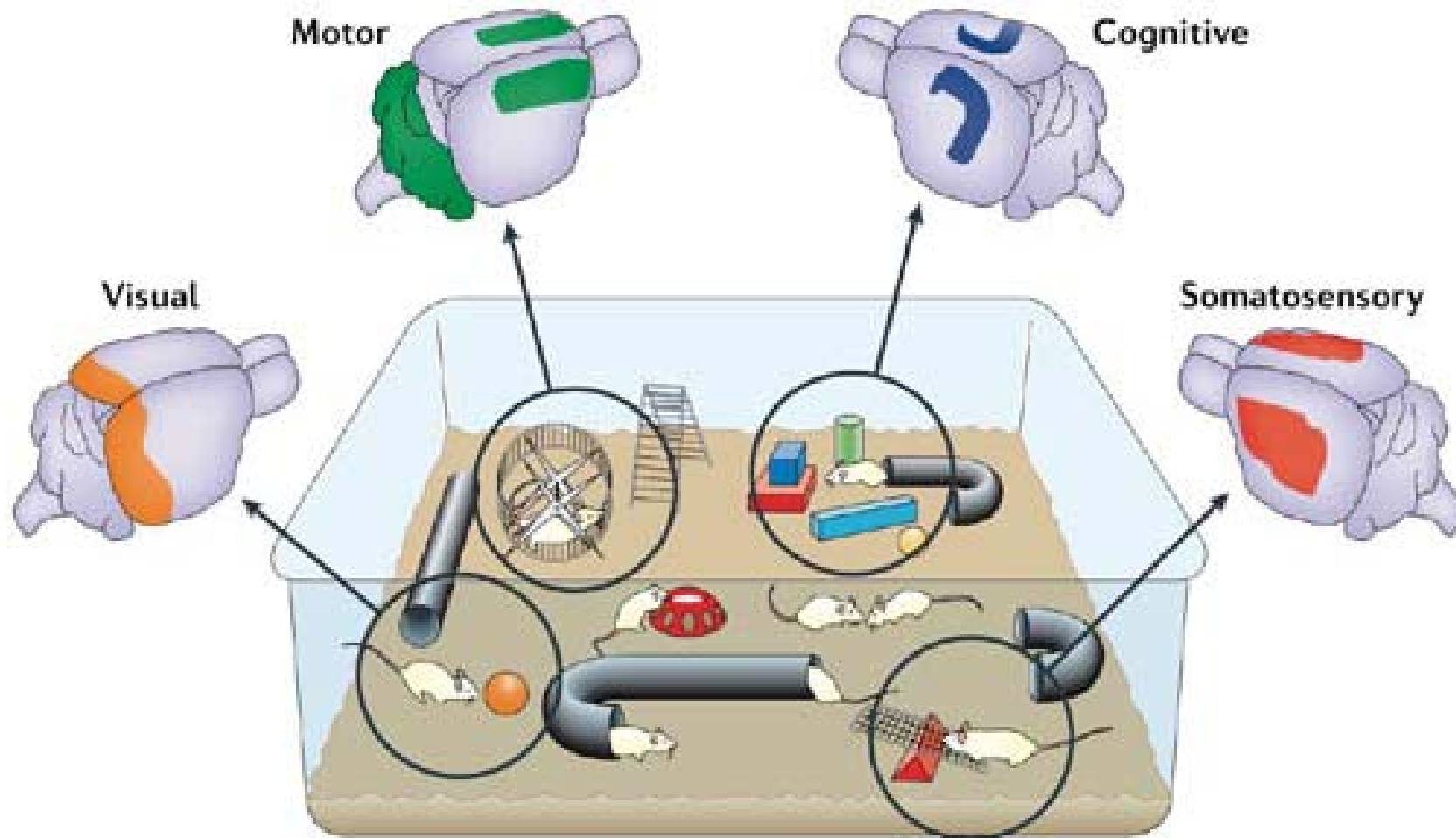


Mouse models of neurodegenerative diseases

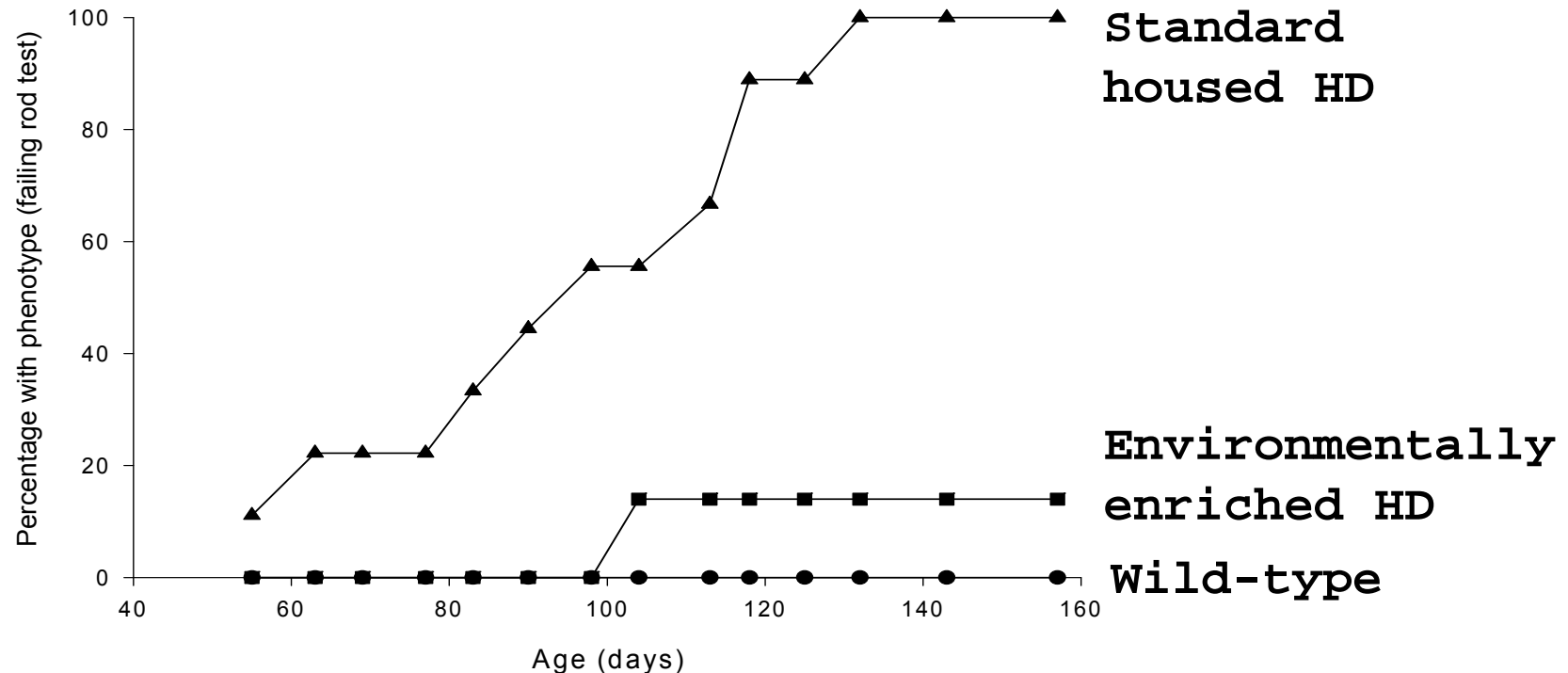
- R6/1 mice expressing human HD transgene encoding expanded polyglutamine (Mangiarini et al., 1996, Cell)
- Progressive neurodegenerative phenotype that closely models human HD



Environmental enrichment enhances activity levels

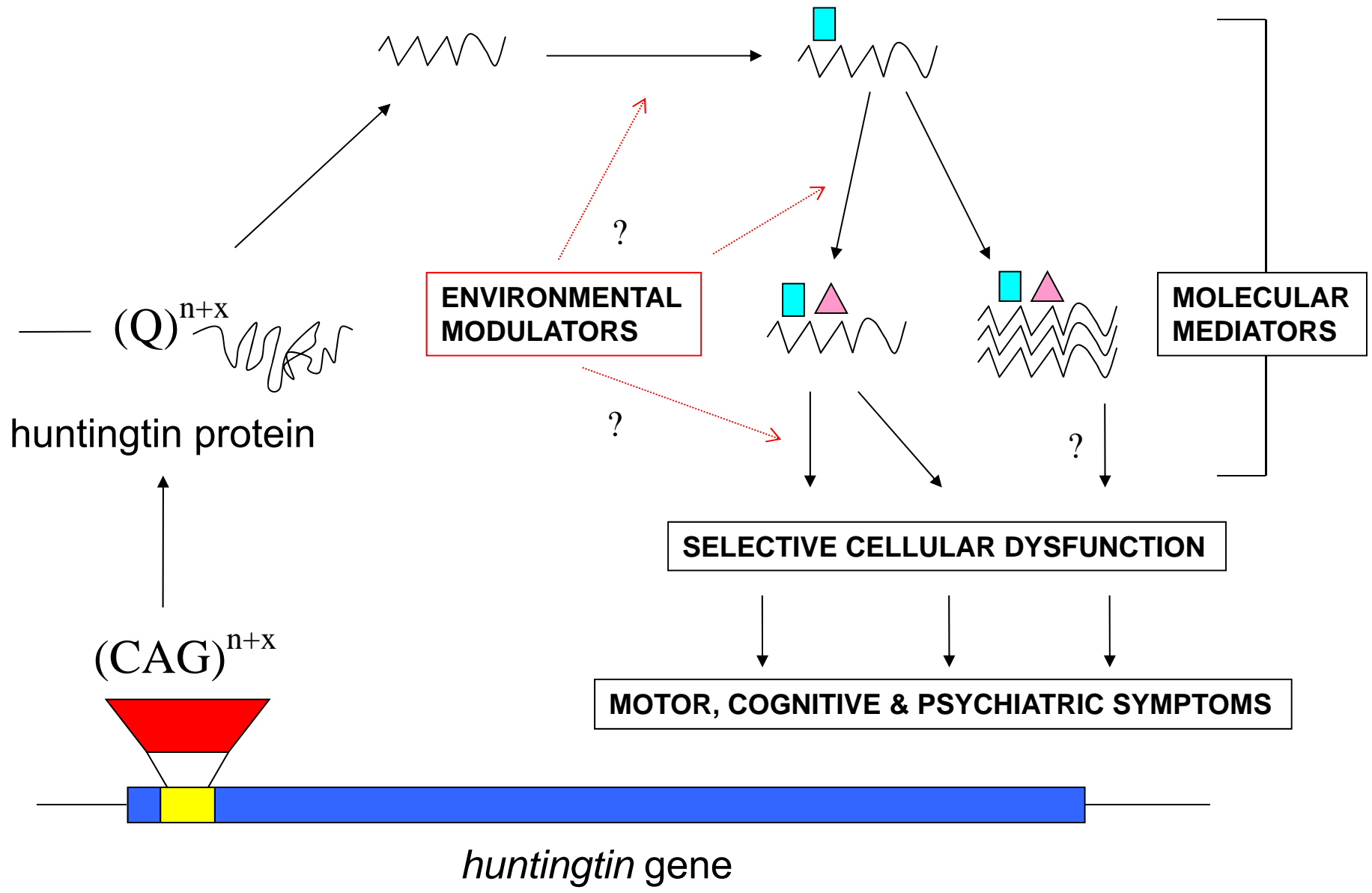


Environmental enrichment delays onset in HD mice



Van Dellen et al., 2000, Nature

Subsequent studies exploring environmental enrichment, cognitive and/or motor stimulation in HD mice: Hockly et al., 2002; 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

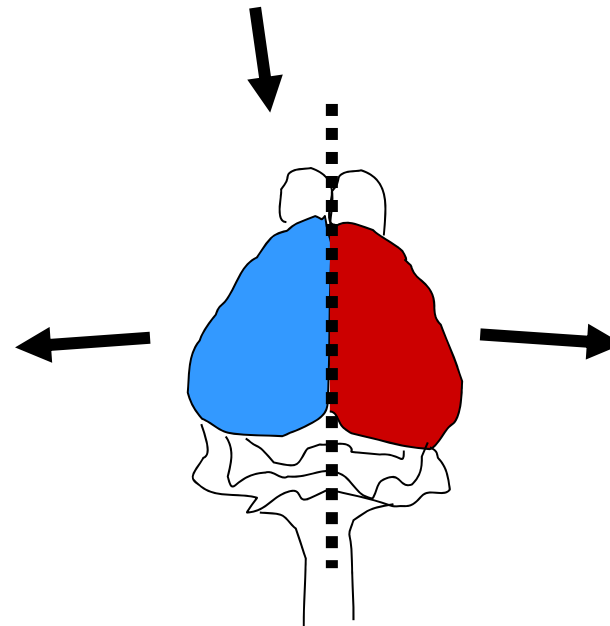


Gene expression profiling in HD and WT mice

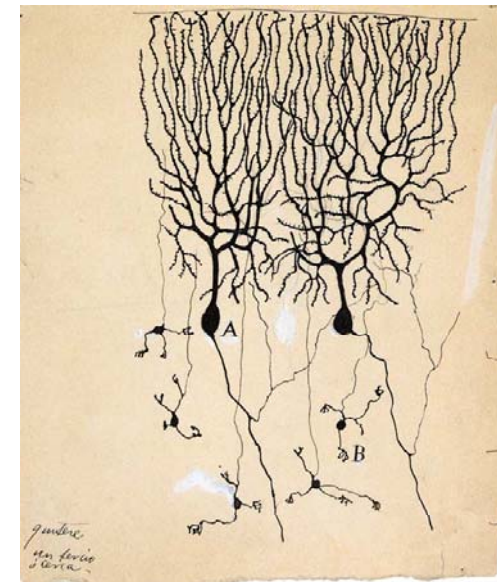
WT and HD mice assigned to standard or enriched conditions

Neocortex
(frontal, parietal, occipital)
Hippocampus
Striatum

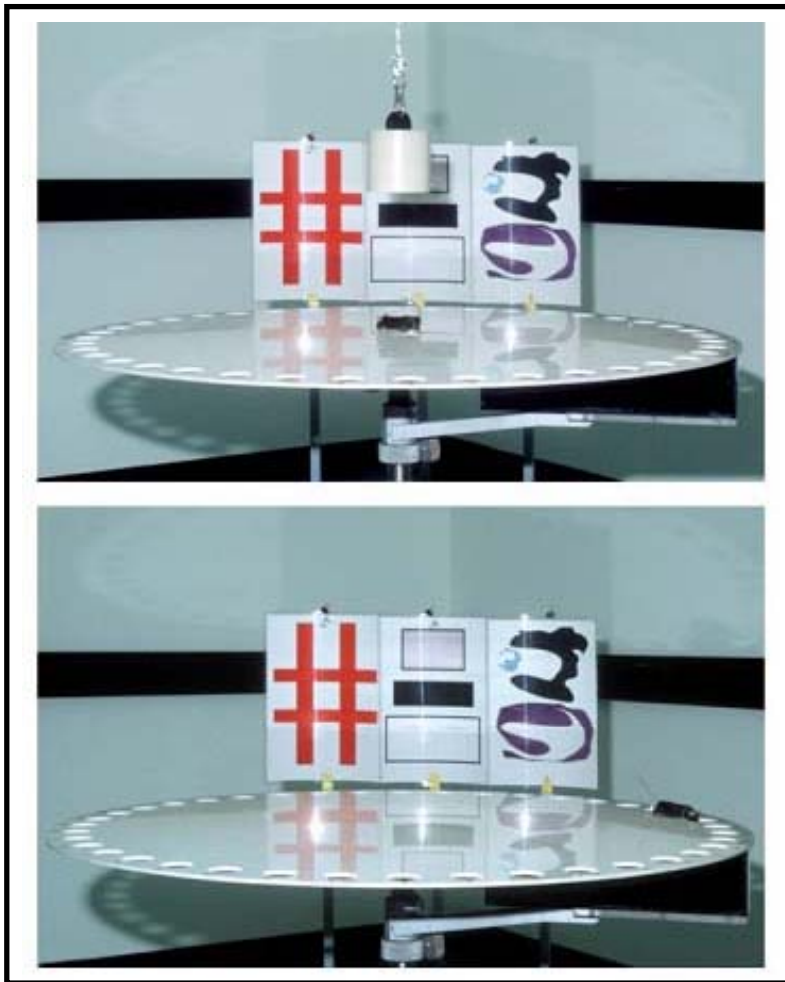
Microarrays, qRT-PCR
ELISA, Western analysis



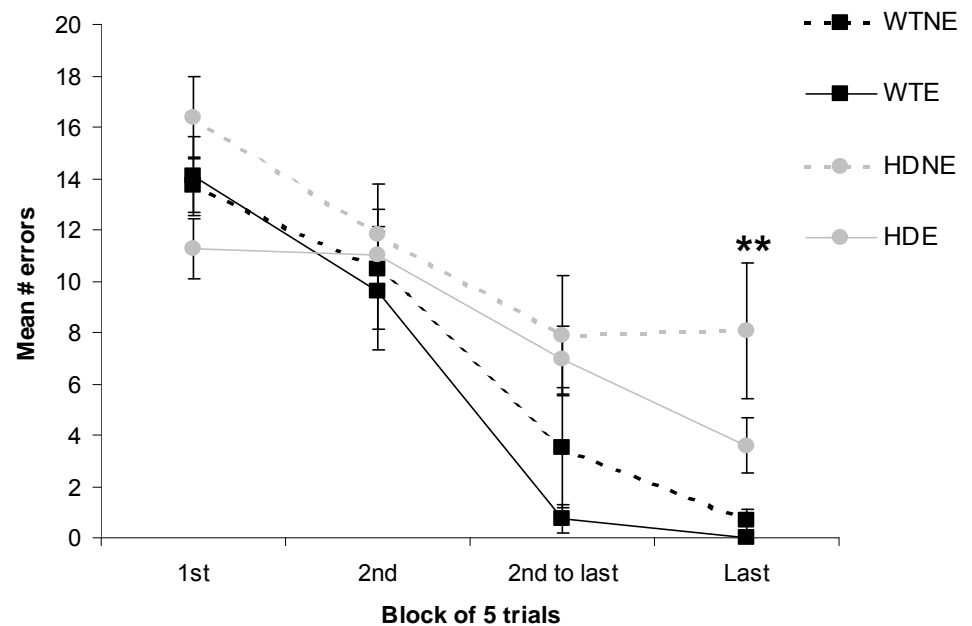
GOLGI & SPINE IMAGING



Environmental enrichment ameliorates spatial learning and memory deficits in HD mice

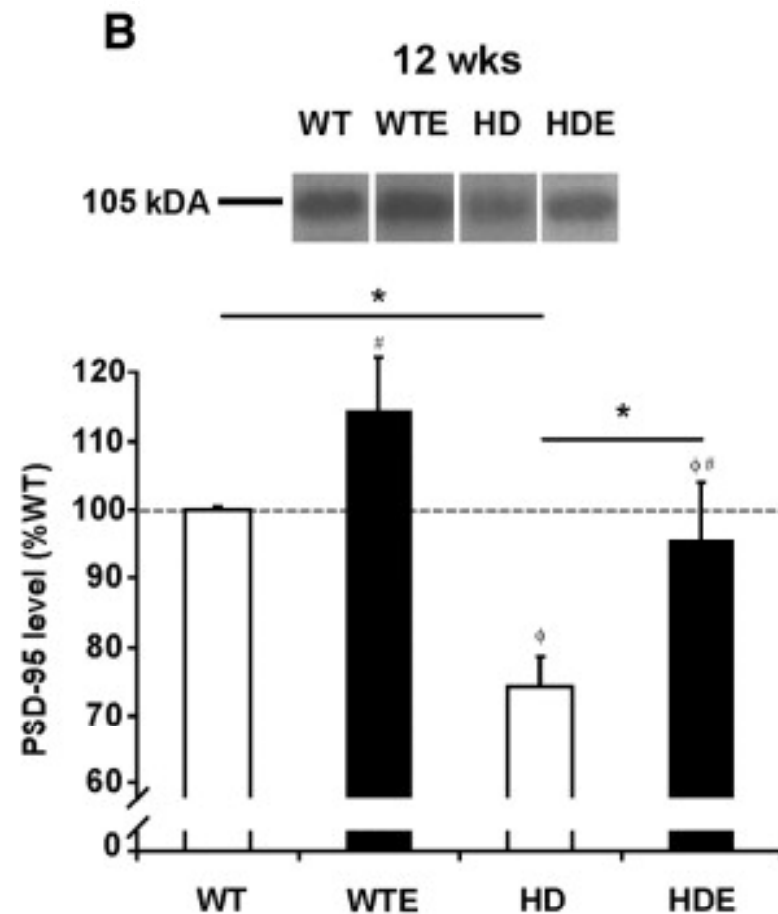
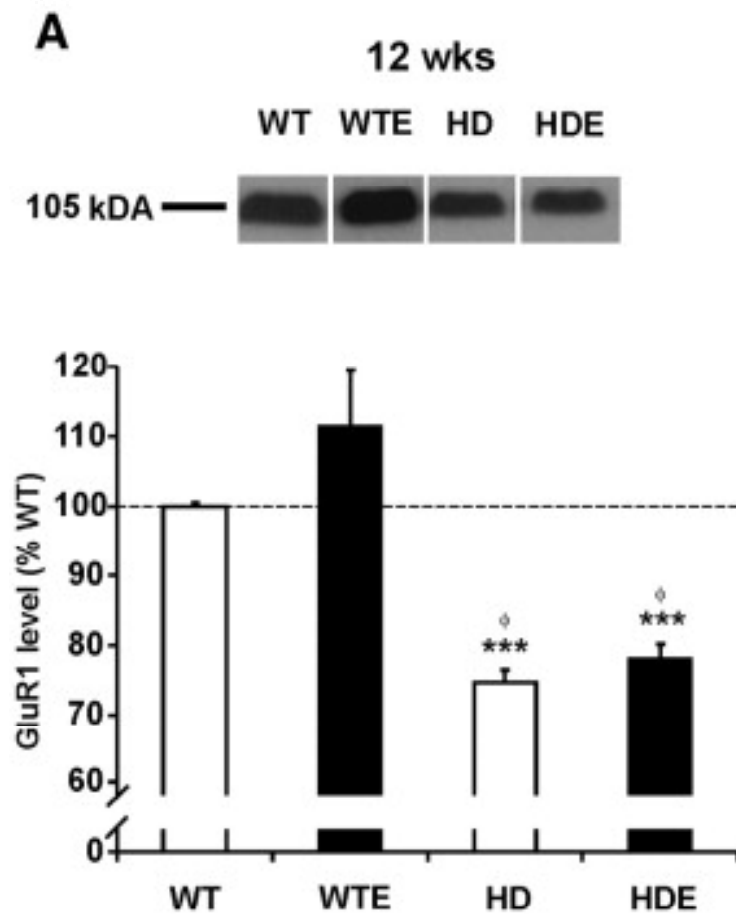


Barnes circular maze

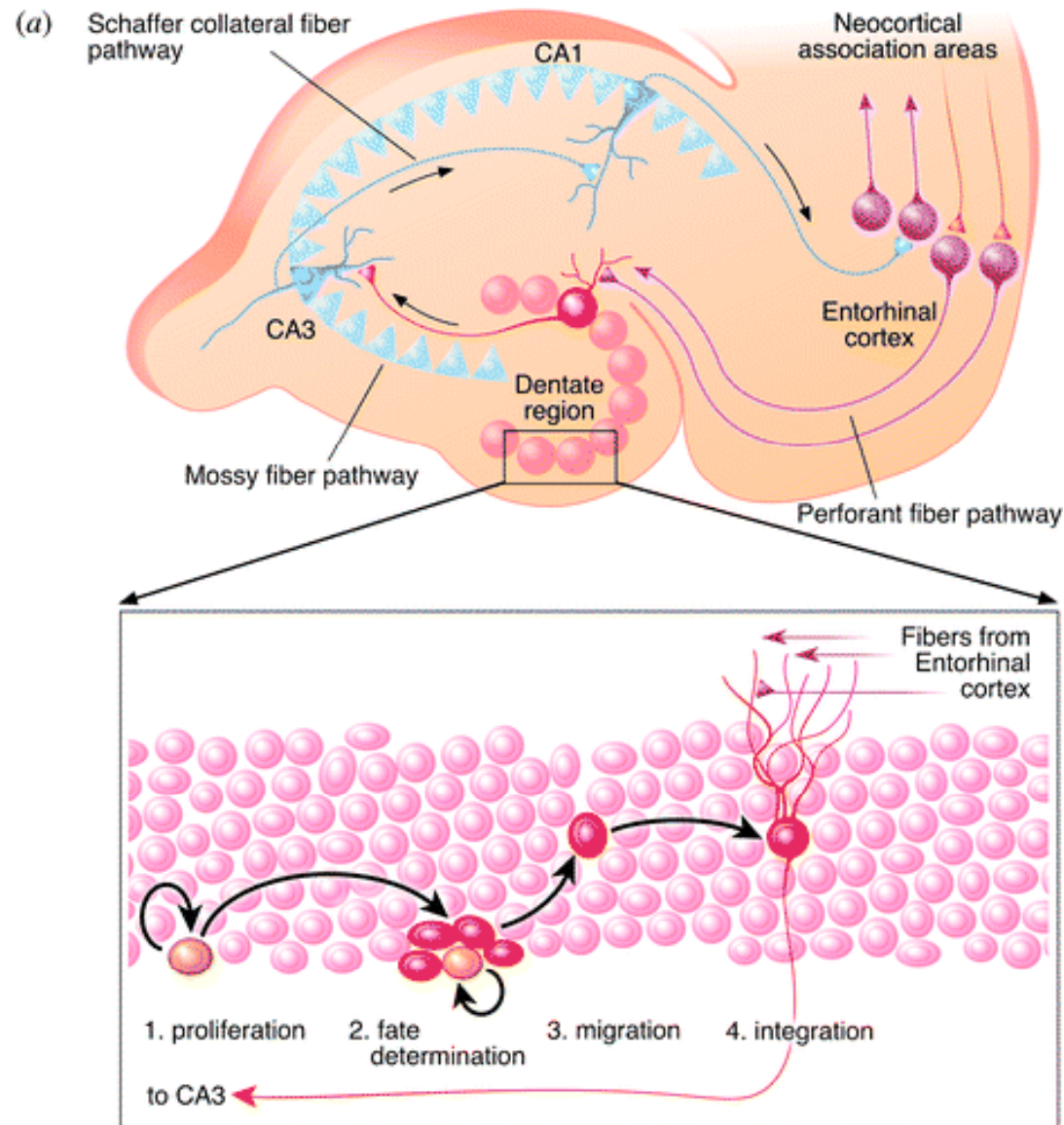


Nithianantharajah et al., 2008, Neurobiol. Dis.

Hippocampal PSD-95 and GluR1 levels are decreased but only PSD-95 is upregulated by enrichment

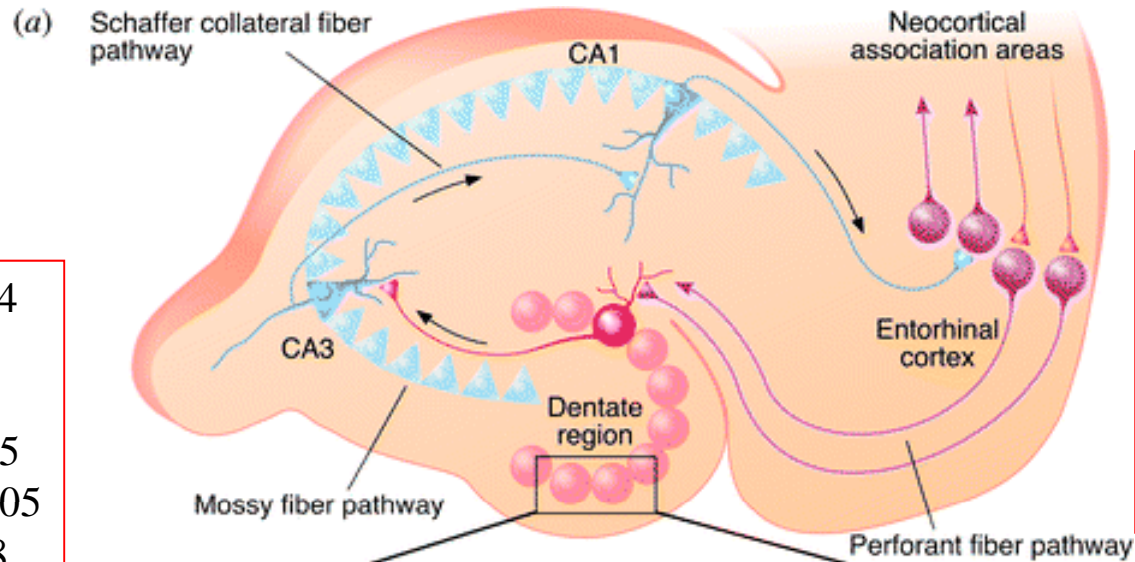


Neurogenesis (birth of new brain cells) may be impaired in dementia and enhanced by mental/physical activity



Lie et al., 2004
Ann. Rev. Pharm. Tox.

Gene-environment interactions and adult neurogenesis



Li et al., 2004

Lazic et al., 2004
Gil et al., 2004
Gil et al., 2005
Grote et al., 2005
Philips et al., 2005
Pang et al., 2008

Kempermann et al., 1997
Van Praag et al., 1999
Malberg et al., 2000
Lazic et al., 2006
Pang et al., 2006
Pang et al., 2008

Genetic & environmental factors
(e.g. HD, 5-HT signaling, BDNF,
glucocorticoids, stress)

Environmental enrichment,
exercise, SSRIs
(e.g. fluoxetine, sertraline)

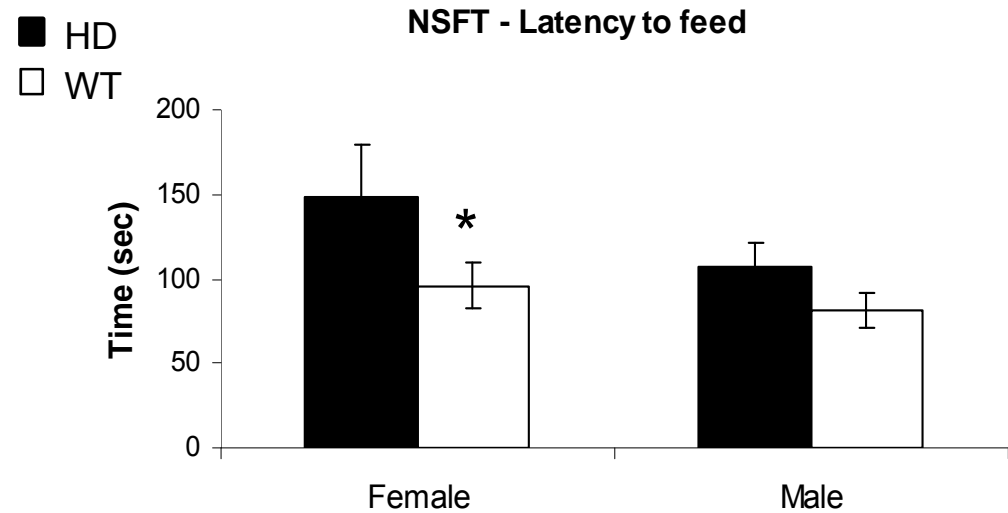
Decreased neurogenesis
Depression/Cognitive deficits?

Increased neurogenesis
Antidepressant/Cognitive effects?

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

Novelty suppressed feeding test (NSFT)

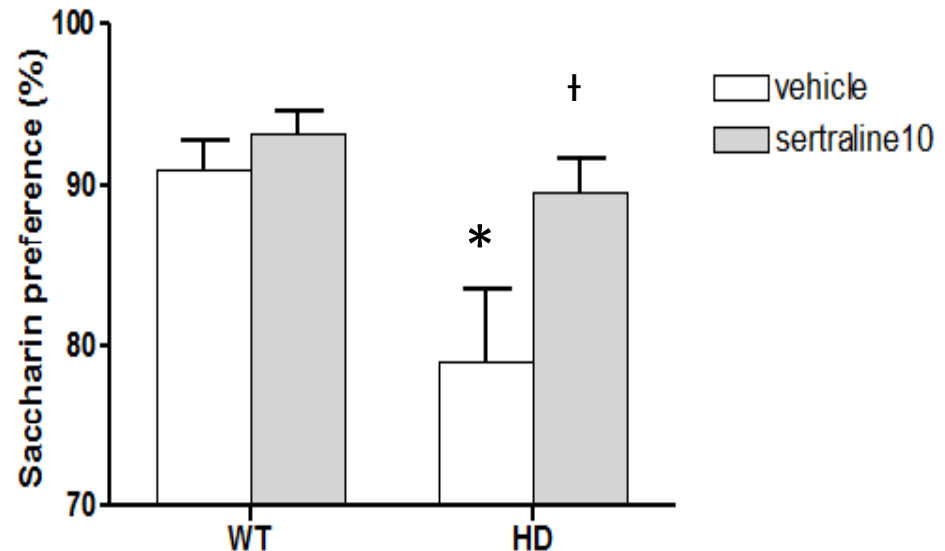
Antidepressants with clinical efficacy rescue this behavioural sign



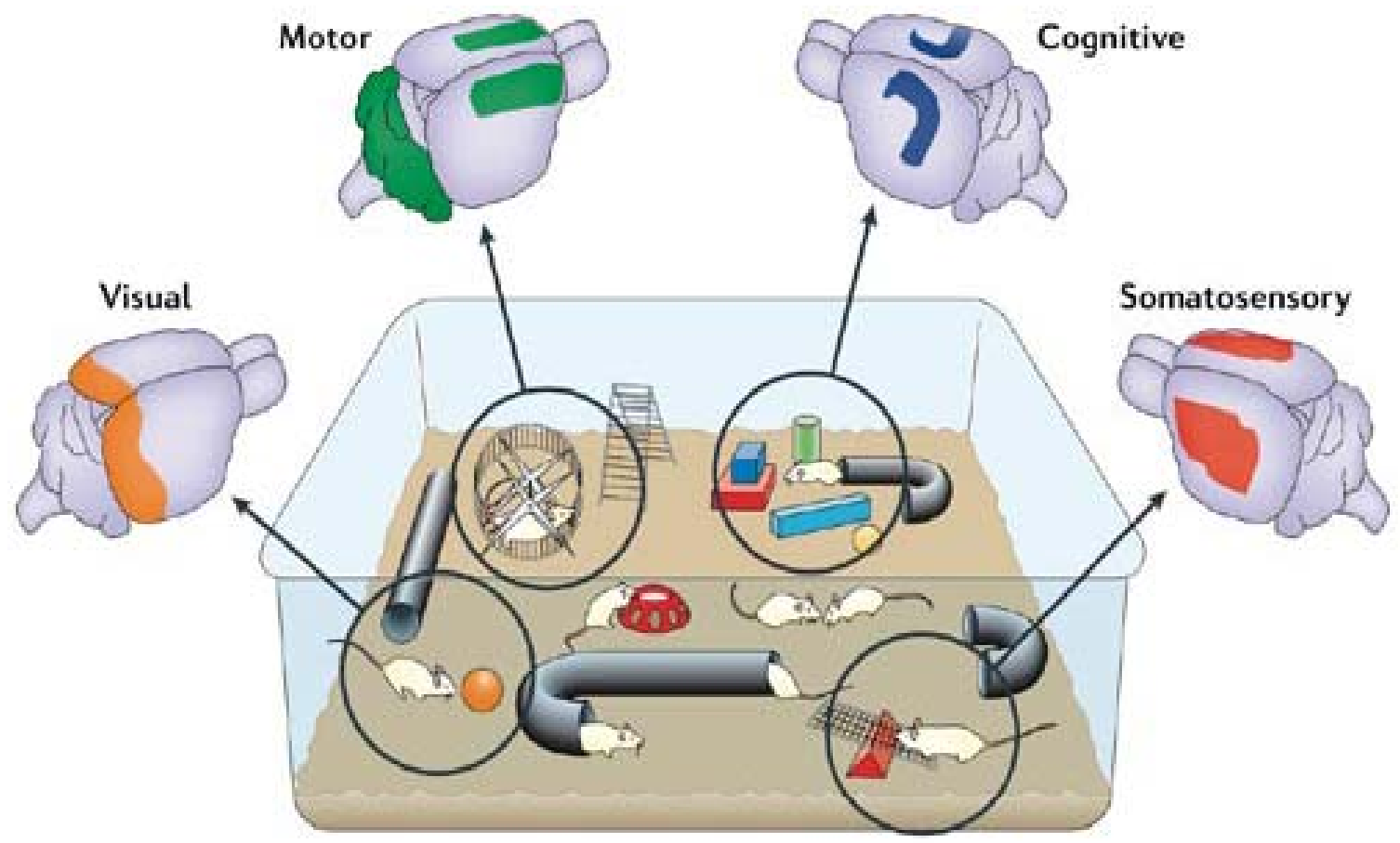
Pang et al., 2009, Hum. Mol. Genet.

Depression-like behaviour in female HD mice is rescued by chronic administration of an antidepressant, and by environmental enrichment and exercise

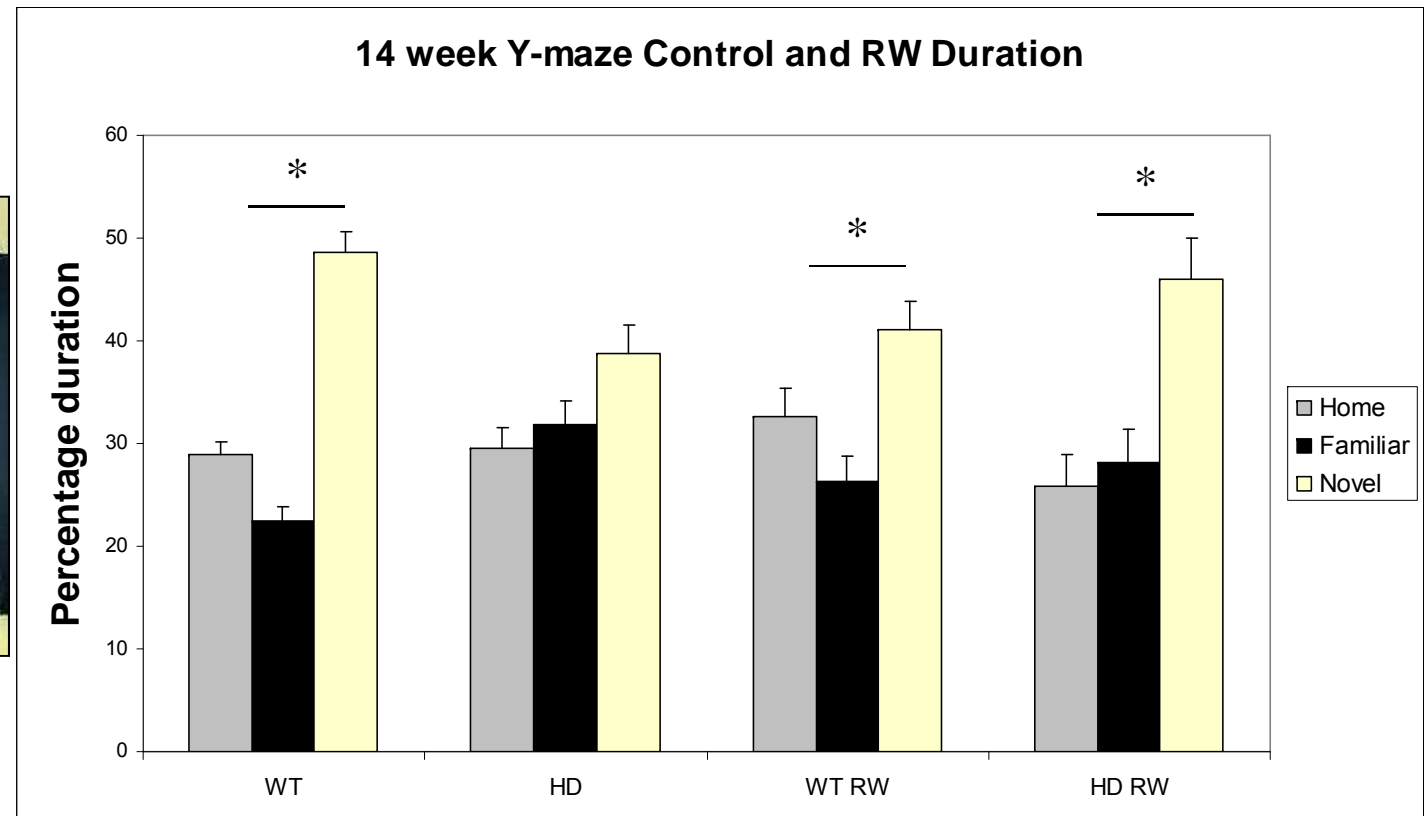
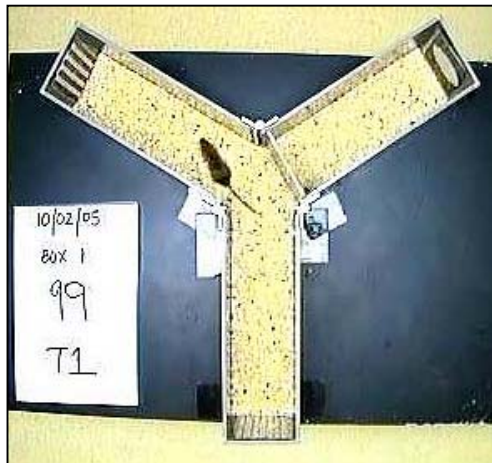
Sacharin-preference test (SPT) of anhedonia



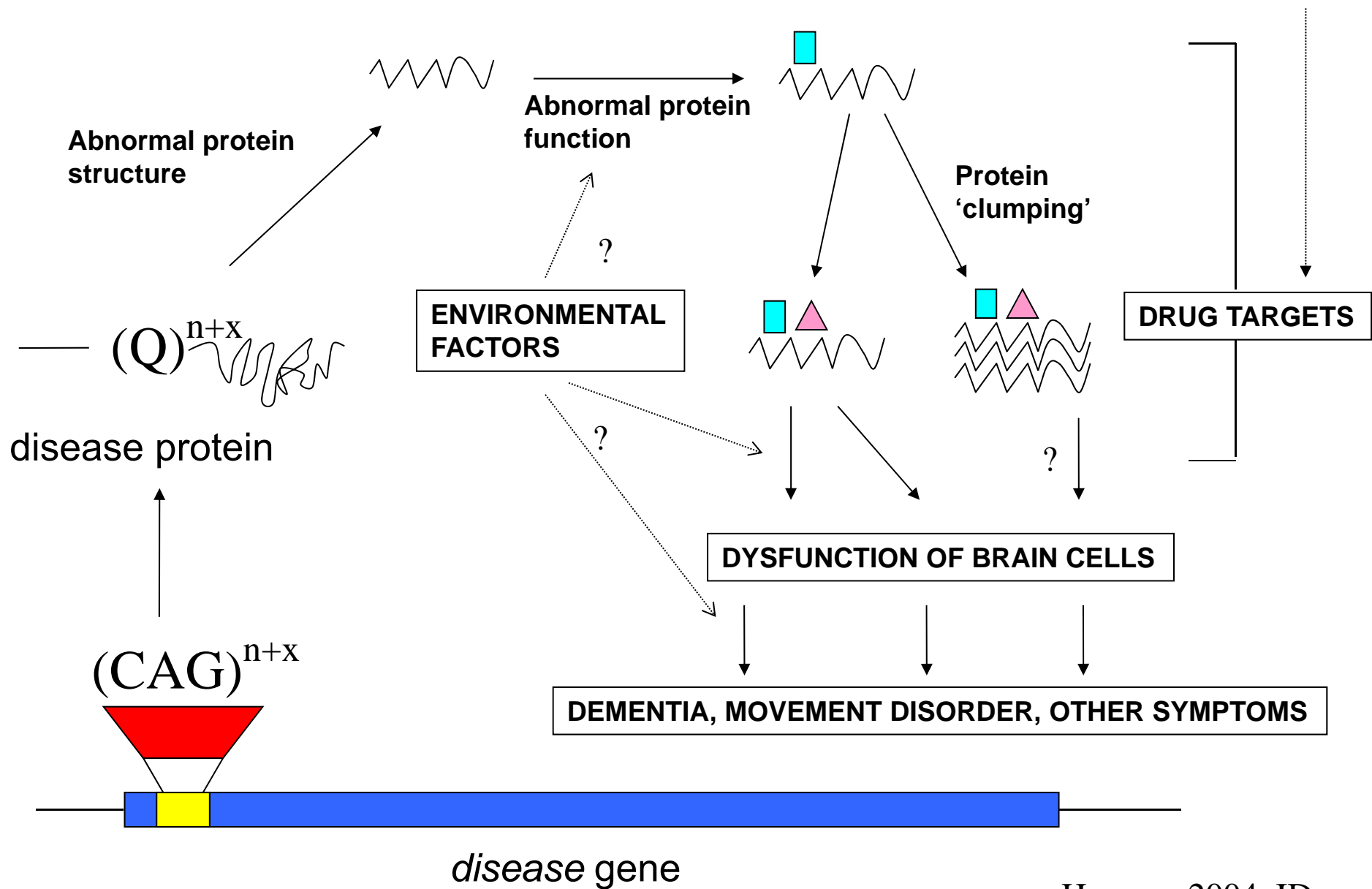
Parsing the components of environmental enrichment: Can enhanced voluntary physical exercise alone induce beneficial effects?



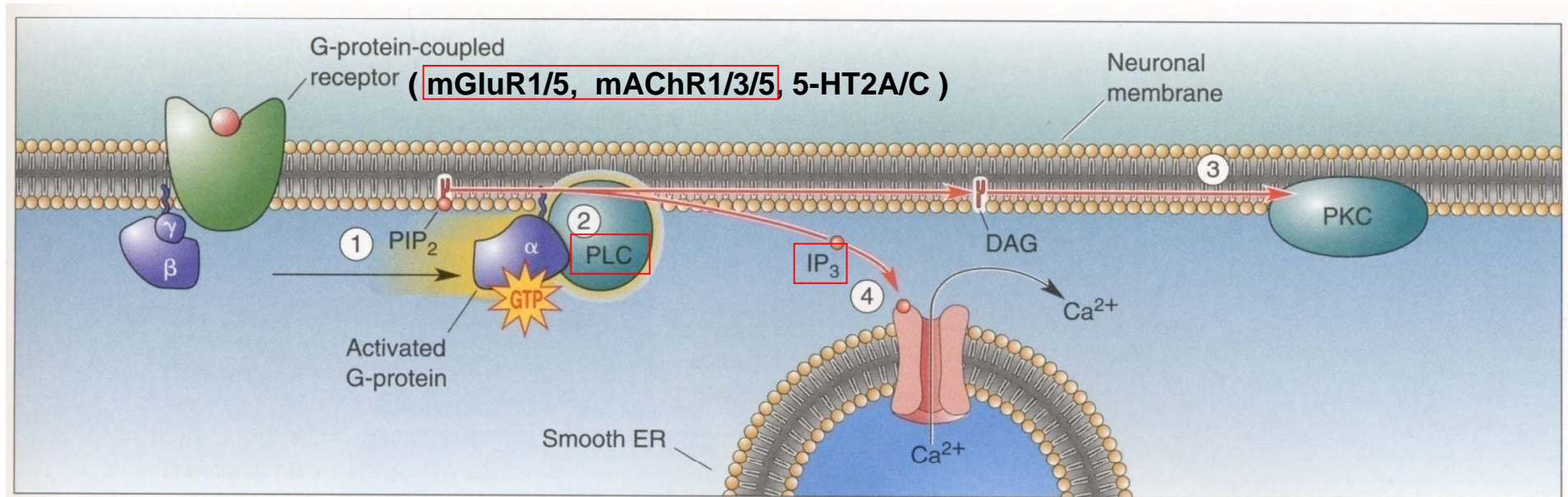
Enhanced physical activity delays the onset of a memory deficit (modeling dementia) in HD mice



DRUGS MIMICKING THE BENEFICIAL EFFECTS OF ENVIRONMENTAL STIMULATION ('ENVIROMIMETICS')



The phospholipase C- β 1 (PLC- β 1) signaling pathway



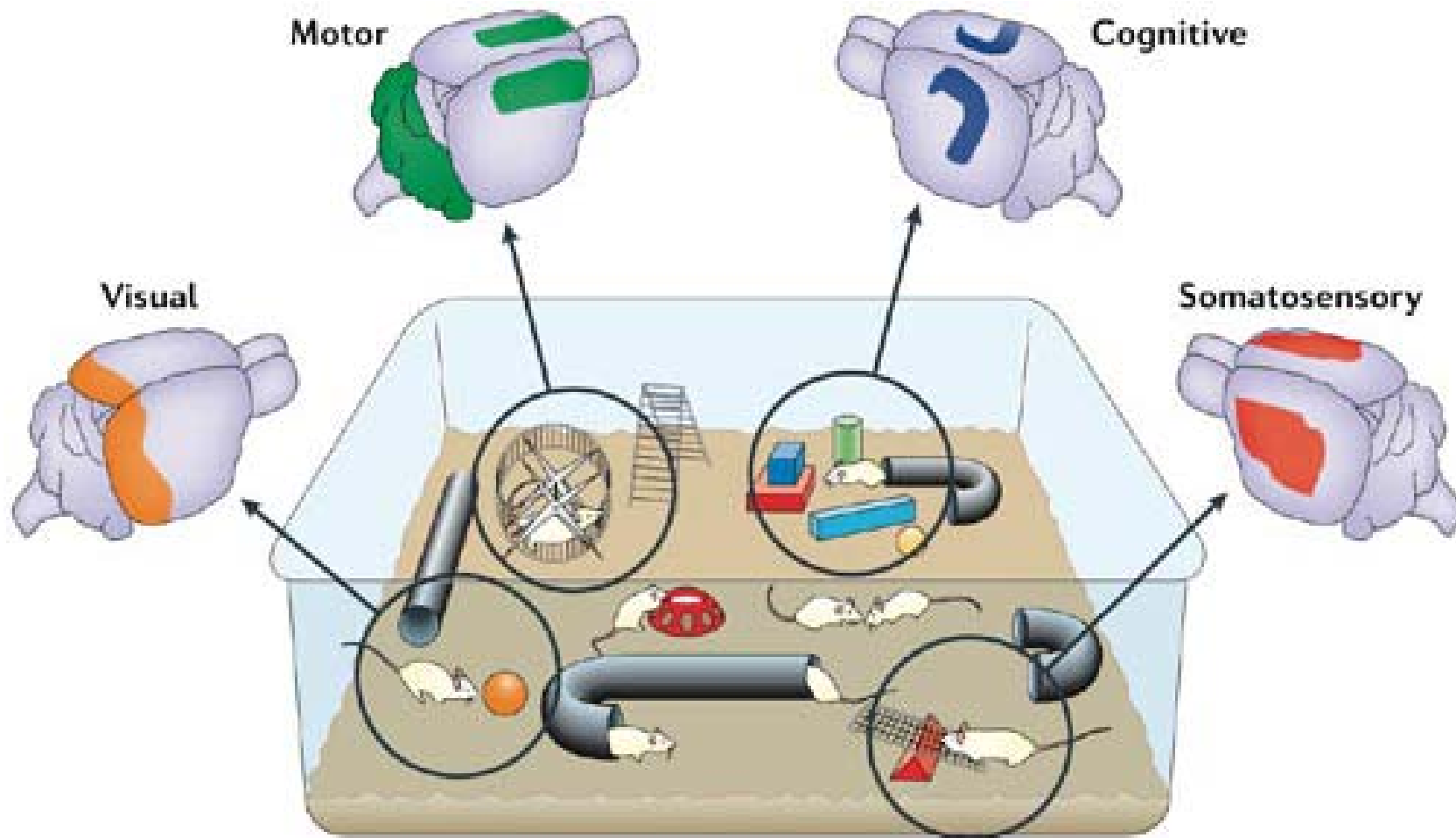
PLC- β 1 and critical periods of postnatal cerebral cortex development and plasticity:

Kind et al., 1997, J. Neurosci.

Hannan et al., 2001, Nature Neurosci.

Spires et al., 2005, Cerebral Cortex

Can environmental enrichment modulate endophenotypes of relevance to schizophrenia?



Nithianantharajah & Hannan, 2006, *Nature Rev. Neurosci.*

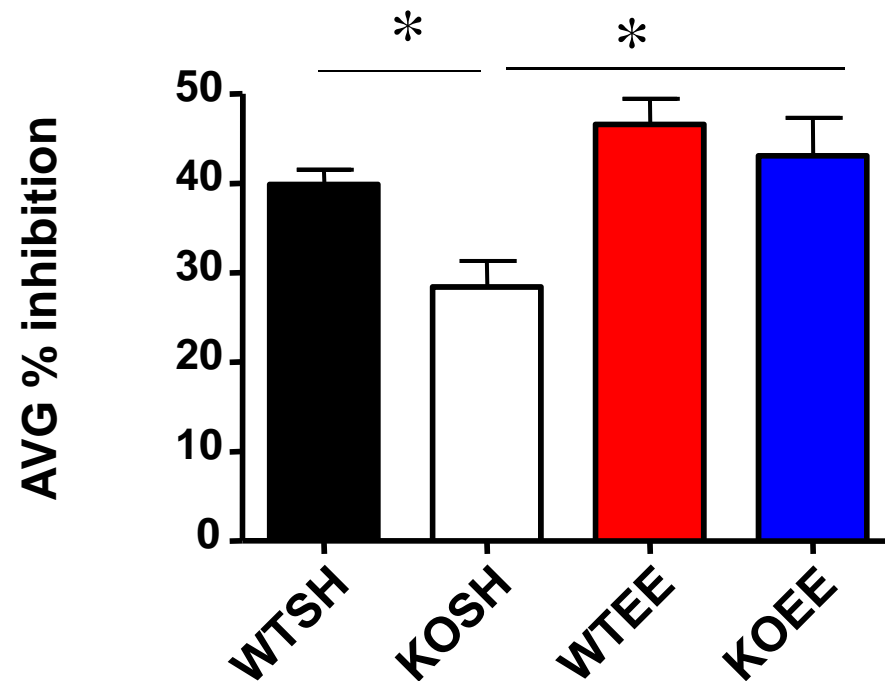
Environmental enrichment rescues a sensorimotor gating deficit in PLC-β1 knockout mice

Prepulse inhibition (PPI) of acoustic startle is a measure of sensorimotor gating used in animal models and humans (deficits have been found in schizophrenia)

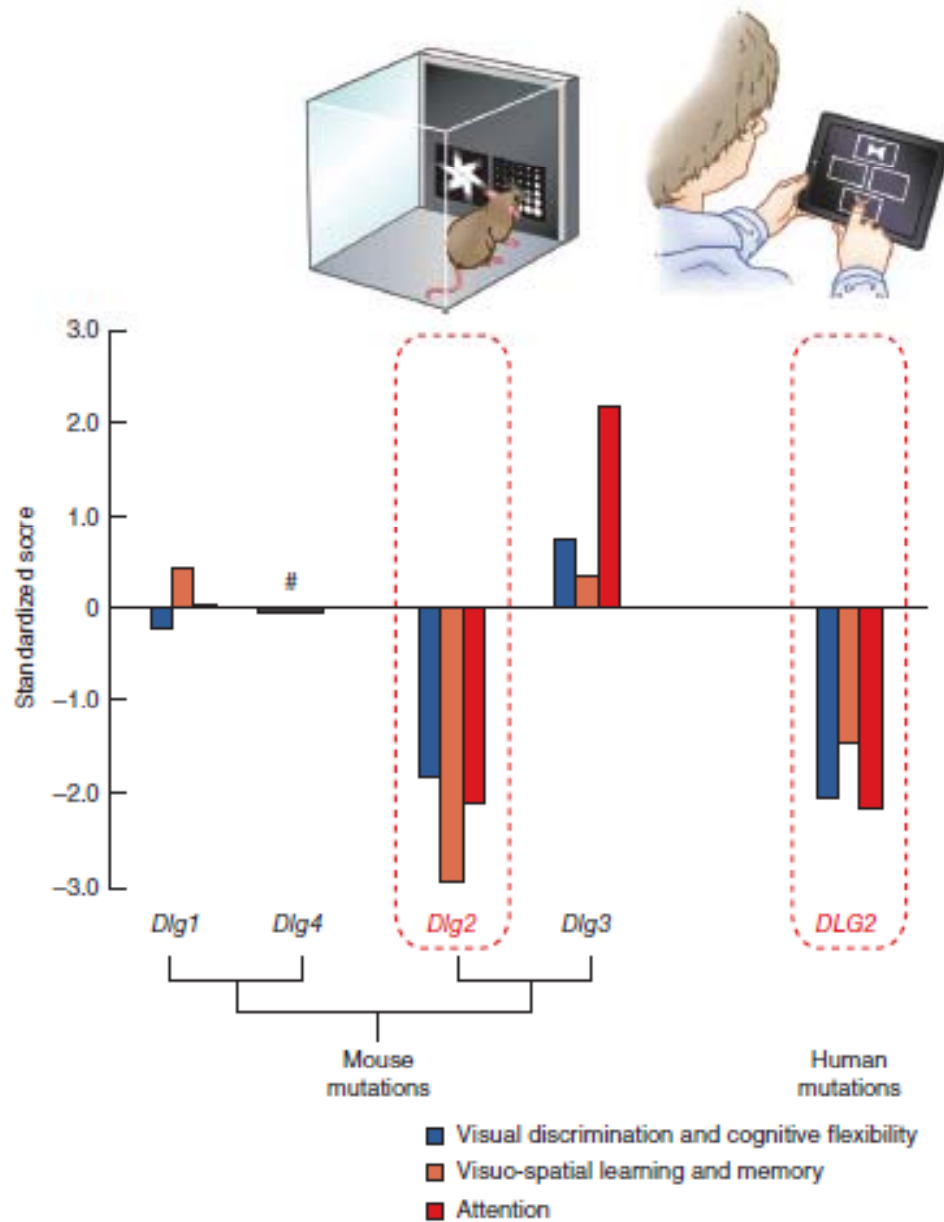
The antipsychotic clozapine also rescues this behavioural deficit



Effect of Environment $p < 0.001$
Effect of Genotype $p < 0.001$
Genotype x Environment $p < 0.05$



Of mice and men (and back again!)



Nithianantharajah et al.,
2013, Nature Neurosci.

Brain Reserve ('Use it or lose it'!)

Neuroprotective brain capacity due to chronic enhancement of mental and physical activity

