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’

DNA

Exon

Intron

Exon

RNA

5’ UTR

Coding region

3’ UTR

5’

Exon

3’

Protein

Fragile X syndrome

Friedreich ataxia

Huntington’s disease

Myotonic dystrophy

Kennedy’s disease

Spinocerebellar ataxias

(CAG) → expansion = disease

Nithianantharajah & Hannan, 2007, Bioessays
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

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
MOLECULAR ENVIRONMENTAL MEDIATORS

huntingtin protein MODULATORS

(CAG)\(^{n+x}\) huntingtin gene

ENVIRONMENTAL MODULATORS

SELECTIVE CELLULAR DYSFUNCTION

MOTOR, COGNITIVE & PSYCHIATRIC SYMPTOMS

Hannan, 2004, IDrugs
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

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.
Gene-environment interactions and adult neurogenesis

- 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?

References:
- 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
- Philips et al., 2005
- Pang et al., 2008
- Grote et al., 2005
- Gil et al., 2004
- Gil et al., 2005
- Lazic et al., 2004
- Li et al., 2004
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

Pang et al., 2009, Hum. Mol. Genet.; Renoir et al., 2012, BJP
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

Pang et al., 2006, Neuroscience
DRUGS MIMICKING THE BENEFICIAL EFFECTS OF ENVIRONMENTAL STIMULATION (‘ENVIROMIMETICS’)

Abnormal protein structure

\[(Q)^{n+x}\]

Abnormal protein function

\[(CAG)^{n+x}\]

disease protein

Abnormal protein 'clumping'

ENVIRONMENTAL FACTORS

DRUG TARGETS

DYSFUNCTION OF BRAIN CELLS

DEMENTIA, MOVEMENT DISORDER, OTHER SYMPTOMS

Hannan, 2004, IDrugs
The phospholipase C-β1 (PLC-β1) signaling pathway

- mGluR1/5, mAChR1/3/5, 5-HT2A/C

PLC-β1 and critical periods of postnatal cerebral cortex development and plasticity:
Spires et al., 2005, Cerebral Cortex
Can environmental enrichment modulate endophenotypes of relevance to schizophrenia?

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

McOmish et al., 2008, Mol. Psychiatry
Of mice and men (and back again!)

Brain Reserve (‘Use it or lose it’!)

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

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<th>Brain Reserve</th>
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<td><strong>Molecular mediators</strong></td>
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<td>• genes &amp; proteins</td>
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<td>‘epigenetics’ (chemical modification of genes)</td>
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GENETIC FACTORS

ENHANCED MENTAL/PHYSICAL ACTIVITY

BRAIN MATURATION & PLASTICITY

OTHER ENVIRONMENTAL FACTORS

PROTECTION VIA BRAIN RESERVE

DYSFUNCTION IN SPECIFIC BRAIN SYSTEMS

FUNCTIONAL COMPENSATION VIA BRAIN RESERVE

FAILURE TO FUNCTIONALLY COMPENSATE

HEALTHY BRAIN FUNCTION & AGING

THERAPEUTICS (e.g. ENVIROMIMETICS)

BRAIN DISORDER SYMPTOMS