Principles of plasticity in the developing brain

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University of Lethbridge, Canada

Take home Message

Preconceptual, prenatal, early postnatal, and adolescent events alter brain development and brain function for a lifetime.

Understanding the nature of these events is important for designing interventions, education, and public policy.

The Questions

How does the brain develop?

How is the development of the brain affected by prenatal and postnatal experiences?

What might the mechanism(s) of the effects be?

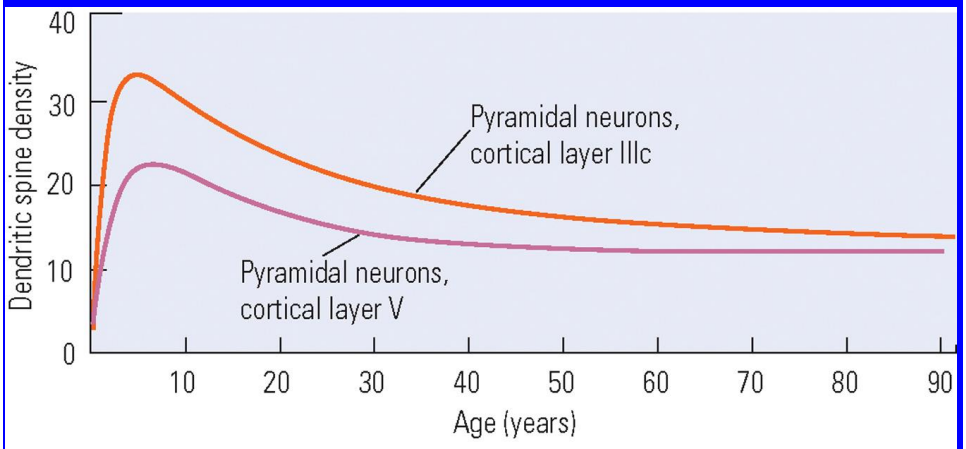
How do early experiences influence later educational/social/health outcomes in children?

Developing the cerebral hemispheres

86 billion neurons
10^{14} connections
=
An engineering marvel…

Your brain is sculpted by a lifetime of experiences, especially in the first few years of life and during adolescence.

Prefrontal Development is Prolonged



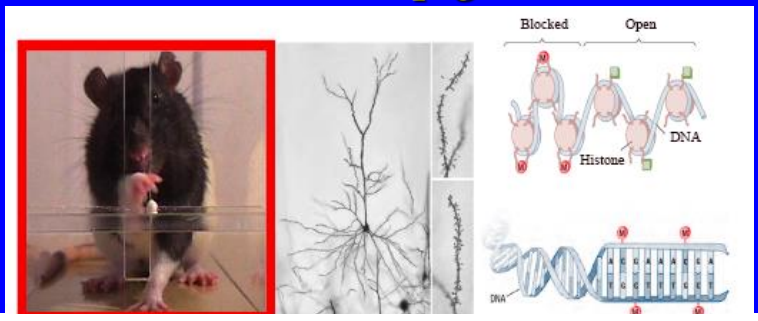
Data source: Petanjek et al., 2011, p. 13283, Figure 2B.

The Logic of Lab Animal Studies

Show functional changes with a wide range of behavioural measures taken at different ages

Infer circuit changes from Golgi stains

Infer mechanisms from epigenetics



What events in brain development are altered by postnatal experience?

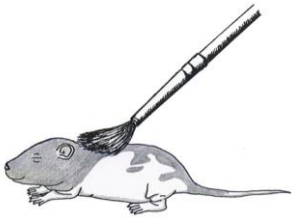
1. Neurogenesis in infant/toddler period.
2. Synapse formation in infant/toddler period.
3. Pruning of cells and connections, especially in early adolescence.

Factors influencing brain development

1. sensory & motor experience
2. language & music
3. poverty
4. pre- and postnatal stress
5. psychoactive drugs
6. parent-child relationships
7. peer relationships
8. diet
9. gut bacteria
10. perinatal injury
11. immune system

Tactile Stimulation

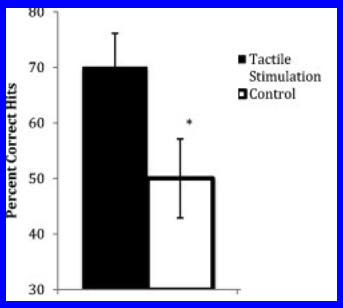
Maternal Massage Kangaroo Care



Both gestational and infant tactile stimulation alter brain and behavioural development.

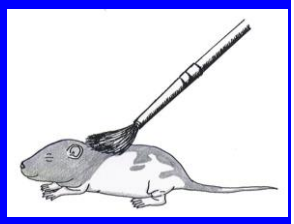
These effects can be seen in the adult brain and behaviour.

Skilled Reaching Success in Adulthood After Infant TS

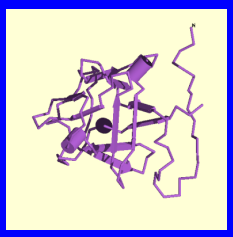


Infant tactile stimulation improves adult motor & cognitive function.

This is correlated with increased synaptic space across the cortex.



How does this work?



FGF-2

Events that alter FGF-2 therefore should influence brain development.
They do.

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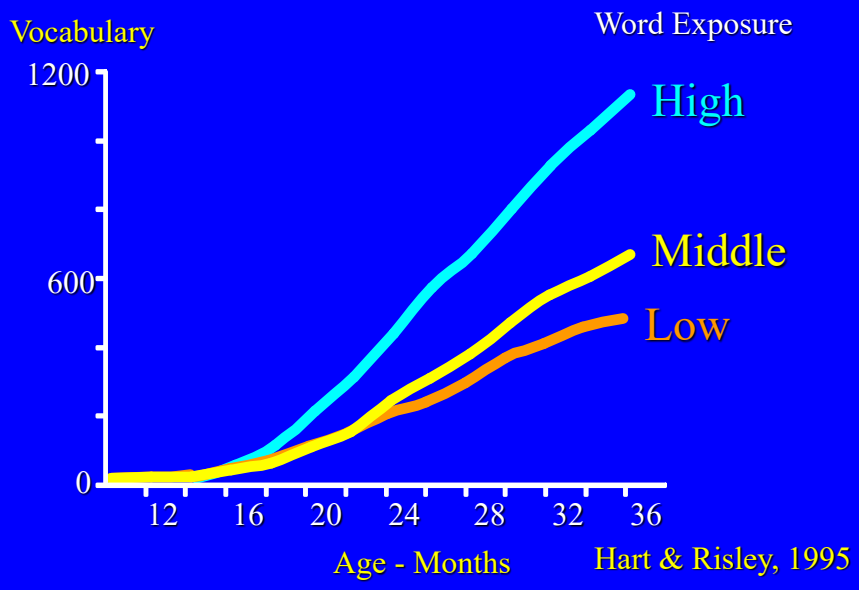
Early Language Exposure Changes the Brain

My main point here is that language and cognitive activity (including music) change the trajectory of developing brain regions, and later behaviour.

Vocabulary Growth – First 3 Years



New Zealand Education Study

Gave reading and mathematics tests to the same children at age 5 & 14.

Result: There was virtually no difference in relative standing – even with 8 years of schooling!

THUS: little change in school outcomes after age 5!

Trajectories are set early…

Early Music Exposure Changes the Brain

Music training increases brain volume,
improves school performance,
increases IQ ~ 7 points

And, increases 'cognitive reserve' in aging…

Factors influencing brain development

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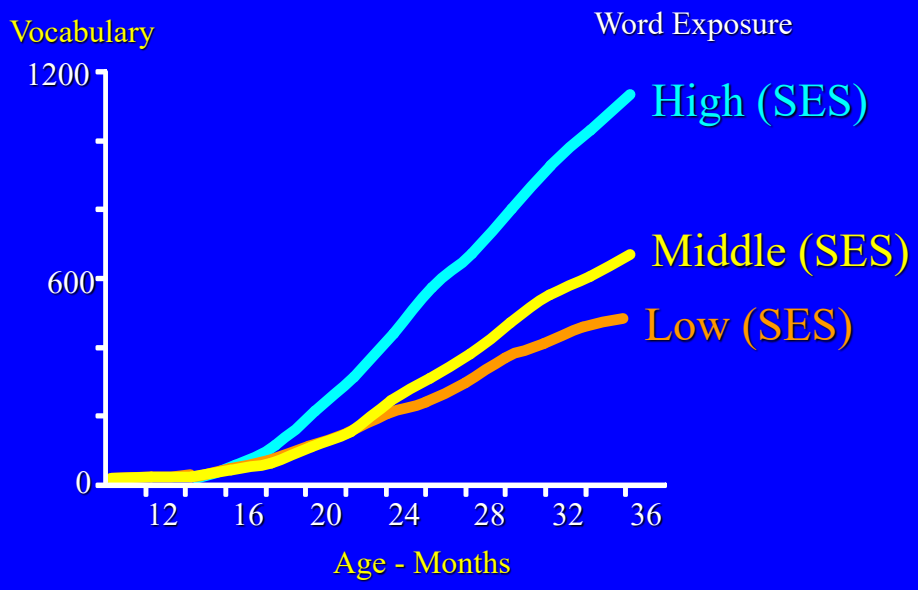
Vocabulary Growth – First 3 Years

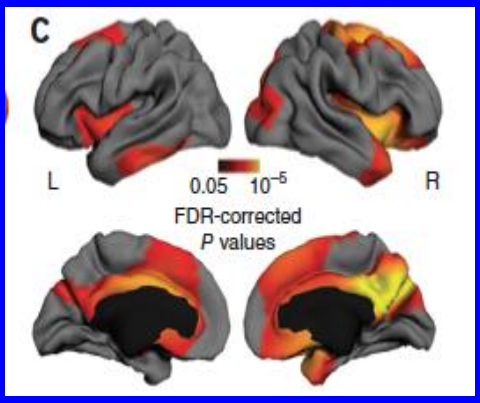


Early Language Exposure Changes the Brain

By age 4, the low SES kids have a 30 million word exposure deficit…

It is not only vocabulary but also grammatical structure that is different… (Erica Hoff, 2003)

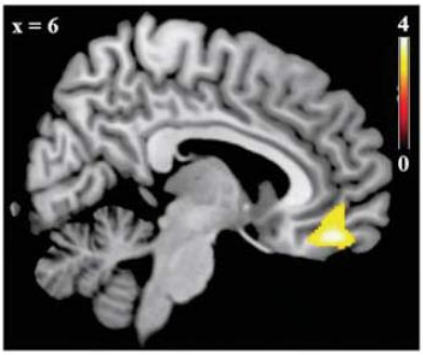
Family income is related to cortical surface area in kids and is related to language development.

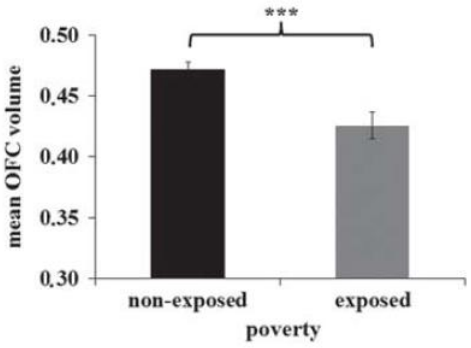


The cutoff for this effect was ~US $40,000

Noble et al (2015). *Nature Neuroscience*, online doi:10.1038/nn.3983.
See also Mackey et al, Psychological Science, Apr 20, 2015 online.

Poverty reduces OFC volume in a 25 year prospective study





Holz et al., Neurpsychopharmacology, 2015

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Adult Stress and PFC

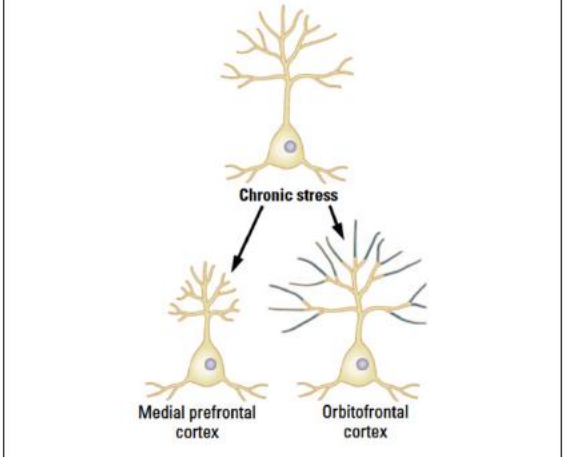


FIGURE 3 | The medial and orbital prefrontal regions show opposite chronic effects of stress in male rats in adulthood. (After McEwen and Morrison, 2013).

Means what?

This recovers with time in young but not older animals…

Models of Stress

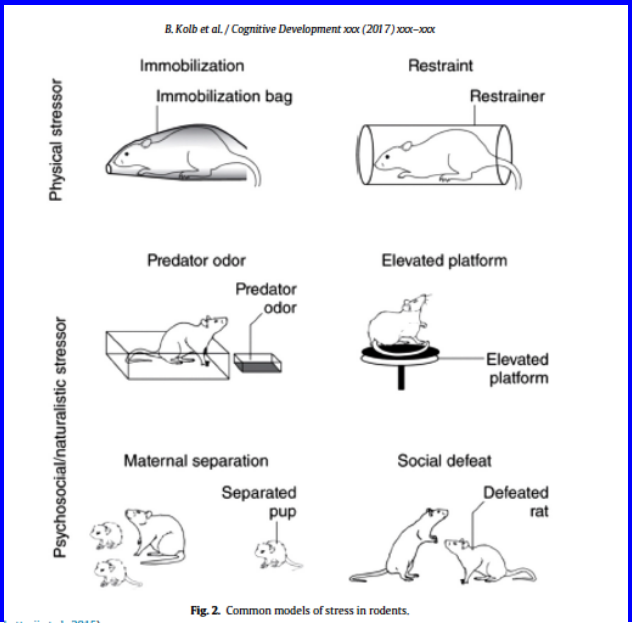


Fig. 2. Common models of stress in rodents.

also: Noise

Gestational Stress

Impaired motor, socio-emotional, & cognitive behaviour in adulthood.

Increased corticosterone levels in adulthood & increased corticosterone reactivity to even mild stressors…

Adult Behavioural Measures

Gestational Stress increases anxiety, especially in males

Gestational Stress feminizes male play

Halliwell, Gibb & Kolb, in progress, 2016

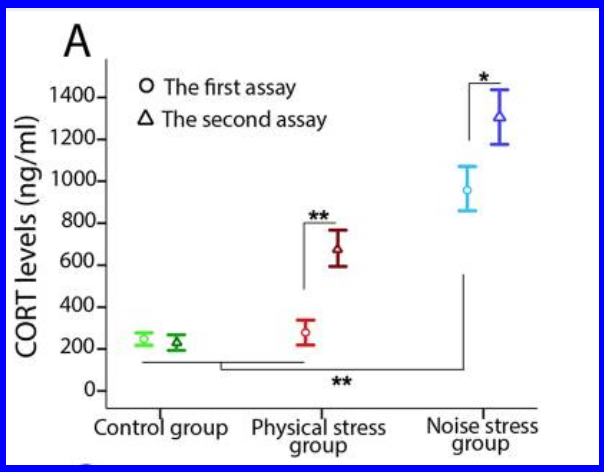
Adult Behavioural Measures

Gestational Stress impairs skilled reaching

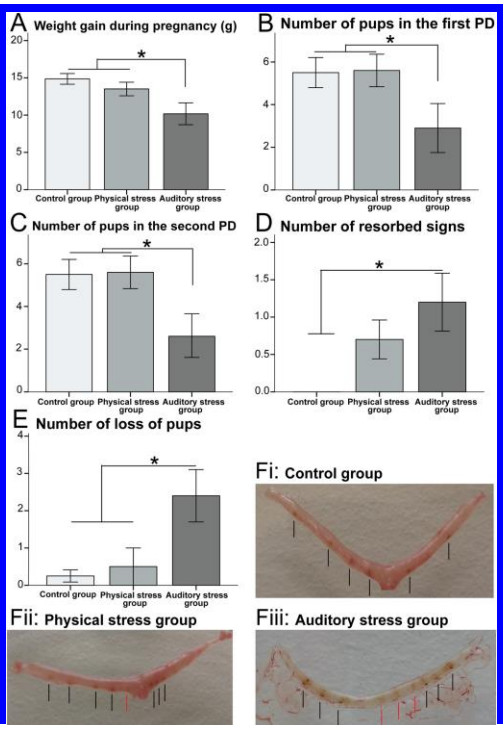
Gestational Stress slows spatial learning

Halliwell, Gibb & Kolb, in progress, 2016

Effects of Gestational Stressors on HPA axis



Jafari et al., Sc Reports, 2017



Gestation stress changes Pregnancy outcome

Jafari et al., Sc Reports, 2017

Jafari et al., Sc Reports, 2017

Effects of Gestational Stress on Brain

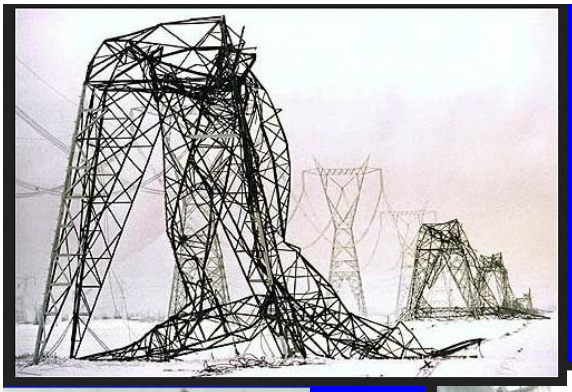
1. *Smaller* brains in adulthood
2. Abnormal connectivity

The Quebec Ice Storm of 1998

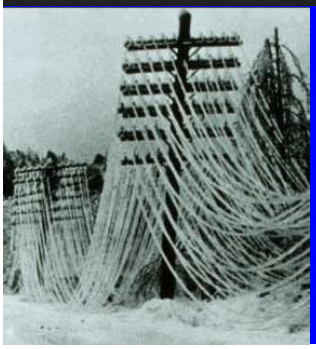
One of the worst natural disasters in Canadian recorded history: power failure for up to 6 weeks in the coldest month of the year (~-20C).

Many pregnant women at various stages of pregnancy and varying degrees of hardship.

Children are being followed with behavior, MRIs, & epigenetics.



Quebec, 1998



The Quebec Ice Storm of 1998

Behavior: cognitive (IQ), linguistic, motor, and play abnormalities measured at 2, 5.5, 8.5, and 11.5 years.

MRIs: still being analyzed

DP Laplante, S King and colleagues

1998 QC Ice Storm and methylation 13 years later

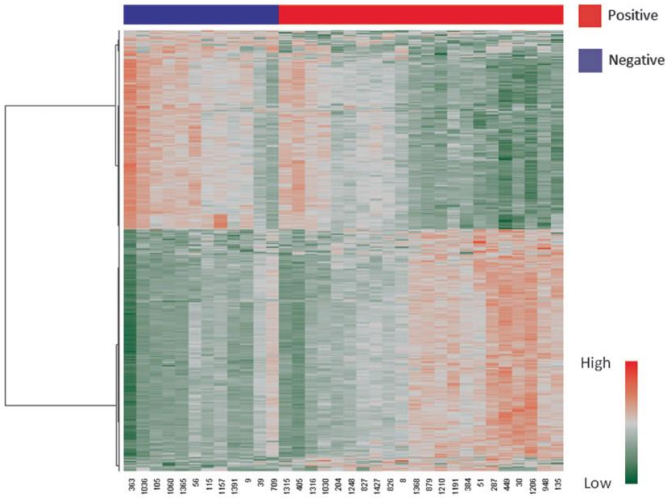
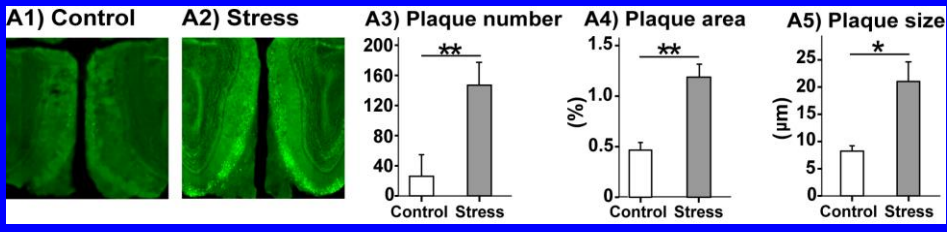


Figure 1. Differentially methylated CGs responding to cognitive appraisal level. Heatmap showing methylation of the 500 most differentially methylated CGs ($P < 0.003$, FDR < 0.055) across all 34 individuals. Each column represents an individual and each row a single CG. A color

Gestational Stress hastens the onset of AD symptoms

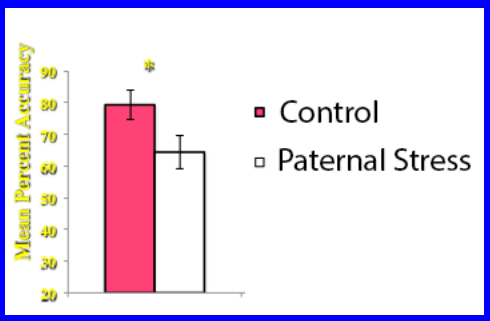


Preconception Stress

Paternal Preconception Stress

30 min 2X per day 27 days prior to mating

Harker et al., *Neuroscience*, 2015



Preconception Stress

The effect of Paternal stress is similar to having a perinatal brain injury…

(e.g., Harker et al., (2015) *Neuroscience*, 303, 200-210.)

Paternal Stress and PFC

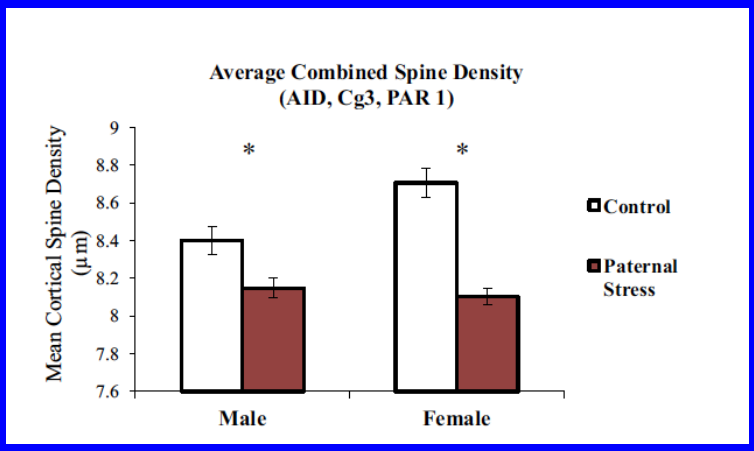
Main overall effect is reduced synaptic space

Biggest changes in OFC
Smallest changes in HPC

Effects are larger in females…
-different than gestational stress where M>F

Proposed to be transferred by noncoding RNAs in sperm…

Golgi Analysis



This is different from adult stress in mPFC

Harker et al., 2015; 2017

Stress Summary

Preconceptual, gestational, and postnatal stress all change behaviour, epigenetics, and neuronal morphology, although in different ways. This is very different from adult stress.

Developmental stress also reduces plasticity later in life.

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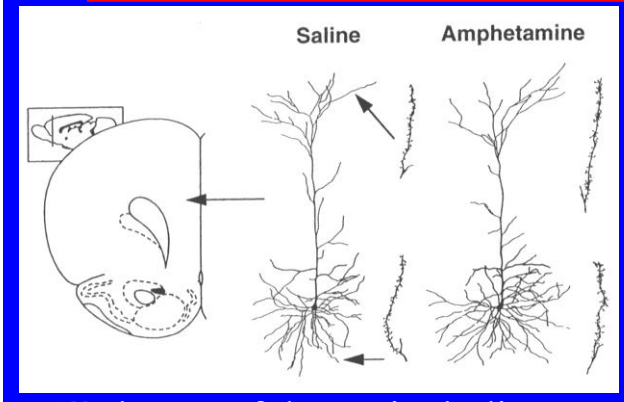
All Psychoactive Drugs Leave a Footprint in the Brain

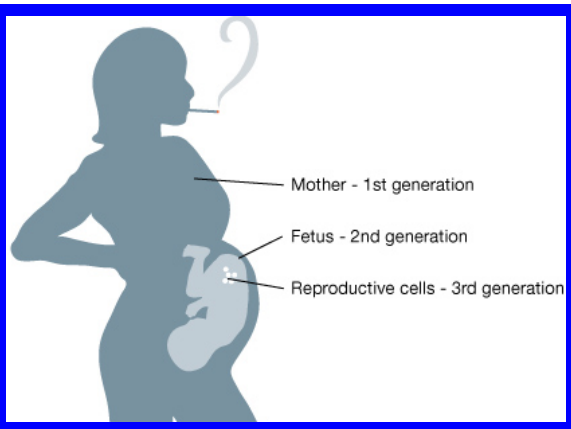


All classes of drugs, including Rx, legal, and illicit drugs change PFC structure & functioning.
Effects are especially large with prenatal exposure.
(see review by Robinson & Kolb, *Neuropharmacol*, 2004)

Early exposure to drugs with chronic effects

- Amphetamine
- Nicotine+
- Caffeine+
- Morphine
- Valproate+
- Antidepressants +
- Methylphenidate
- Alcohol+
- Antipsychotics+
- Anxiolytics+

+and prenatally



Prenatal nicotine is associated with an increased response to nicotine and reduced cerebral plasticity in adulthood.

Fluoxetine (Prozac) is worse!
E.G. Muhammad et al., *Synapse*, 2012

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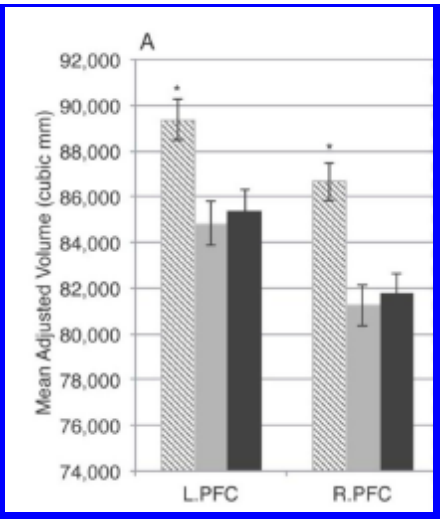
Foreign Adoption Studies

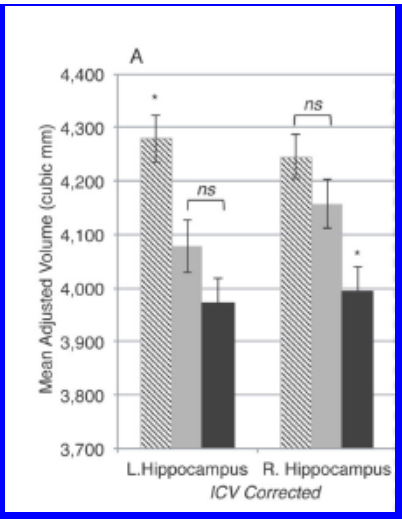
Neuroimage. 2015 January 15; 105: 112–119. doi:10.1016/j.neuroimage.2014.10.020.

Duration of Early Adversity and Structural Brain Development in Post-Institutionalized Adolescents

Amanda S. Hodel, Ruskin H. Hunt, Raquel A. Cowell[1], Sara E. Van Den Heuvel, Megan R. Gunnar, and Kathleen M. Thomas
Institute of Child Development, University of Minnesota, 51 East River Road, Minneapolis, MN, 55455, USA

Children adopted at mean age of 12 mo. MRIs at 12-14 years.





Prefrontal Volume **Hippocampal Volume**

Grey: early adoption Black: late adoption

Behaviour?

Parallel studies have shown reduced IQs and cognitive and socioemotional deficits that are related to age at adoption and length of time in the SAME foster home.

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Play is a Form of Problem-based Learning

What does play do to the brain?

1. increases the 'pruning' in prefrontal cortex.

2. Increases later flexibility (plasticity) in prefrontal cortex.

Bell et al., *Beh Brain Res*, 2010, 207, 7-13.
Himmler et al., *Neurosc Lett*, 2013, 556, 42-45.
Himmler et al., Synapse, in press.

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Leung et al. BMC Pregnancy and Childbirth 2011, 11:12
http://www.biomedcentral.com/1471-2393/11/12

BMC Pregnancy & Childbirth

RESEARCH ARTICLE Open Access

Does prenatal micronutrient supplementation improve children's mental development? A systematic review

Brenda MY Leung[1,2*†], Kristin P Wiens[2†], Bonnie J Kaplan[1,2†]

YES

Factors influencing brain development

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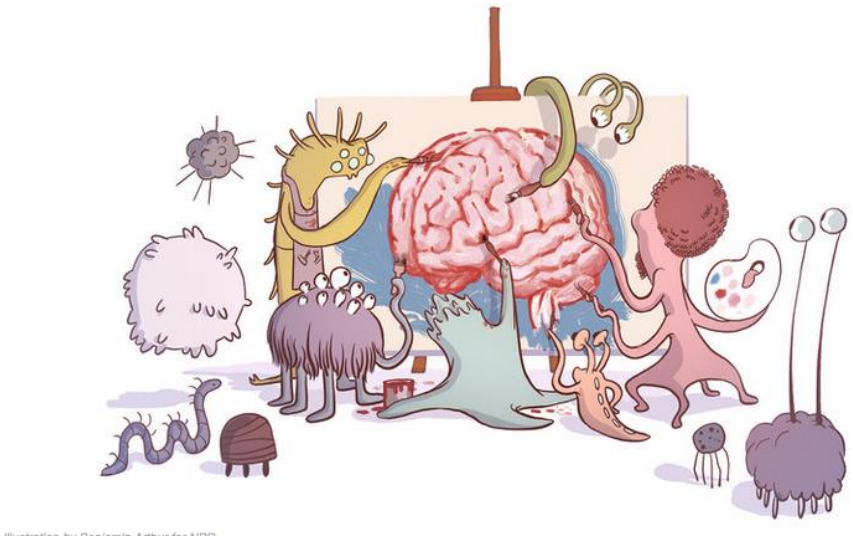

The bugs influence the brain

Microorganisms can alter the Brain

Review

Nature Reviews Neuroscience **13**, 701-712 (October 2012) | doi:10.1038/

Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour

John F. Cryan & Timothy G. Dinan

Biol Psychiatry. 2013 Nov 15;74(10):720-6. doi: 10.1016/j.biopsych.2013.05

Psychobiotics: a novel class of psychotropic.

Dinan TG[1], Stanton C, Cryan JF.

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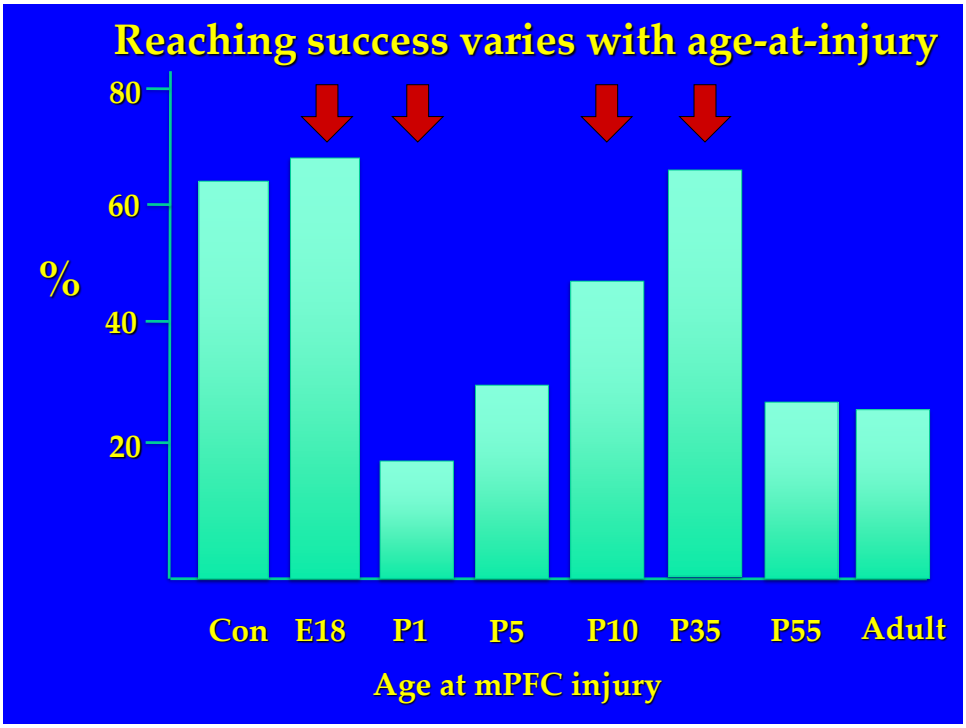
Perinatal Brain Injuries

Outcomes vary with age at injury, age at assessment, behaviour(s) measured, and sex.

The brain is always smaller but at some times there is compensation allowing the brain to do 'more with less.'



Perinatal Brain Injuries

Bottom line is that outcome is related to the precise time of brain development at injury (prenatal, infant, juvenile, early vs late adolescent, adult) and age at assessment.

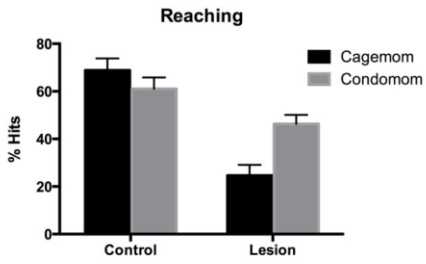
There appear to be several distinct epochs… This is also true of cats, monkeys, & humans

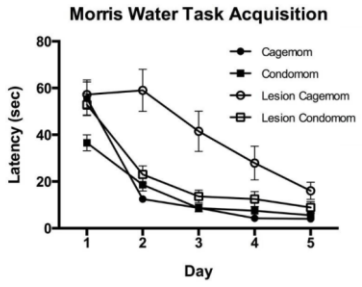
See review by Kolb et al., *Progress in Brain Res*, 2013, 207, 35-64.

Perinatal Brain Injuries

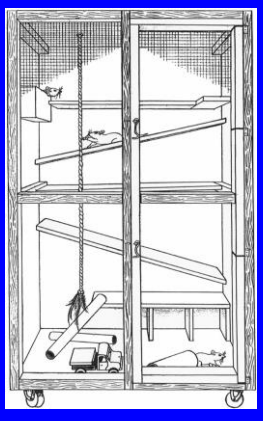
Interventions make a difference: e.g., Tactile stimulation & complex housing.

See review by Kolb et al., *Progress in Brain Res*, 2013, 207, 35-64.





Housing pregnant moms in 'Condos' enhances Recovery from neonatal mPFC injury.



Perinatal Brain Injuries

Recovery is correlated with spontaneous neurogenesis, exuberant connections, synaptic space, & thalamic size.

See review by Kolb et al., *Progress in Brain Res*, 2013, 207, 35-64.

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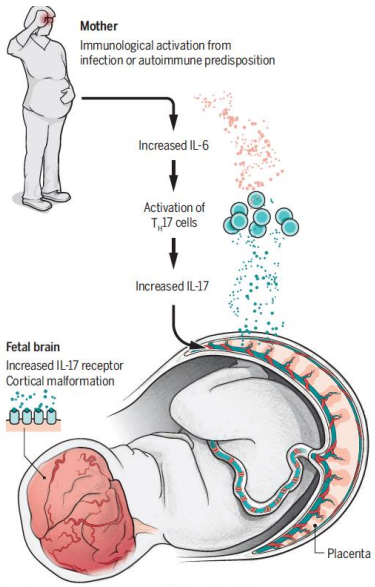
Immune Proteins & Development

Many proteins 1st found in the immune system are also expressed in the developing CNS.



Maternal immune activation (MIA). The hypothetical model shown is based on mouse experiments and illustrates that MIA, possibly in combination with a predisposition for autoimmunity, leads to an increase in T_H17 cells in maternal blood. These cells release IL-17, which crosses the placenta and increases expression of the IL-17 receptor in the offspring's brain. This in turn leads to ASD-related cortical and behavioral abnormalities in the offspring.

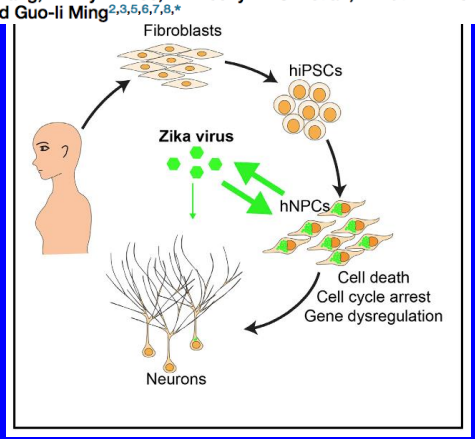
Activation of the immune system proposed in many disorders including ASD, Zika virus and schizophrenia.

e.g., Estes & McAllister, *Science*, 2016, 351, 919-920.

Cell Stem Cell
Brief Report

Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth

Hengli Tang,[1,11,*] Christy Hammack,[1,11] Sarah C. Ogden,[1,11] Zhexing Wen,[2,3,11] Xuyu Qian,[2,4,11] Yujing Li,[9] Bing Yao,[9] Jaehoon Shin,[2,5] Feiran Zhang,[9] Emily M. Lee,[1] Kimberly M. Christian,[2,3] Ruth A. Didier,[10] Peng Jin,[9] Hongjun Song,[2,3,5,6,7,*] and Guo-li Ming[2,3,5,6,7,8,*]



HEAD SIZE IN MICROCEPHALY

Conclusions

Brain development is complex & prolonged.

Brain plasticity in development is influenced by a wide range of early experiences including both pre- and postnatal experiences that may have good, bad, or ugly consequences.

Special Thanks to

Cathy Carroll
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Loni Harker
Yilin Li
Arif Muhammad
Richelle Mychasiuk
Fraser Mustard
Kehe Xie





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Norlien Foundation
CIFAR
CANADIAN INSTITUTE for ADVANCED RESEARCH