New directions integrating genetic, environment, and possible epigenetic effects to understand causes of ADHD

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DISCLOSURES

- Royalties from Guilford Press
  - Getting Ahead of ADHD (2017)
  - What Causes ADHD (2007)
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  - unrestricted philanthropic gifts.

OUTLINE

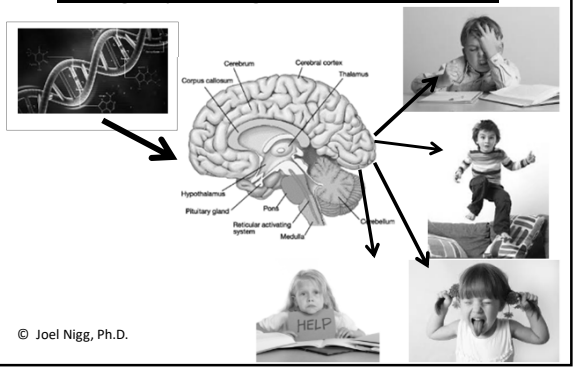
- Plausibility of an epigenetic model or paradigm for ADHD
  - Lessons from complex disease studies
- What exactly is epigenetic change?
- Are environmental correlates of ADHD causal?
  - Using genetically informed studies as one approach to find out
- Preliminary human DNA methylation findings in ADHD
- Conclusions

PLAUSIBILITY OF AN EPIGENETIC PARADIGM FOR ADHD

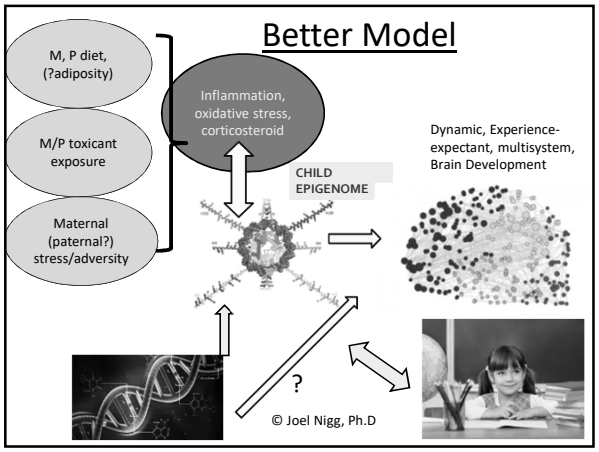
What is the paradigm?

- Paradigm=exemplar (Aristotle, Kuhn)
- Wrong paradigm 1: metabolic disease
  - "find the gene, solve the disease"
- Wrong paradigm 2: Linear causality
  - "like a machine; mass=force x acceleration. Find the causal chain, solve the disease"

OLD VIEW combined those two ideas into a single paradigms(1980s-2000's)



Better Model



3 reasons to reconsider the environment and integrate it with our progress in genetics

- Complex disease model more appropriate
- GxE (heritability of liability) hidden in heritability
- Epigenetic insight— GxE determines phenotype biologically (if not always statistically)

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Simple versus complex disease: Is it "genetic"? What does that mean?

- Single gene disorder
- Complex disease

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Simple versus complex disease: Is it "genetic"? What does that mean?

- Single gene disorder
- Deterministic
- Rare (< 1/10,000)
- Large risk increase in relatives
- PKU, Huntingtons'

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Simple versus complex disease: Is it "genetic"? What does that mean?

- Single gene disorder
- Deterministic
- Rare (< 1/10,000)
- Large risk increase in relatives
- PKU, Huntingtons'
- Complex disease
- Probabilistic
- Common (> 1/500)
- Small risk increase in relatives
- Hypertension

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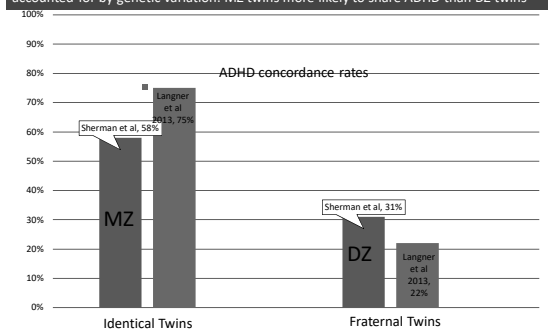
"Heritability" of ADHD is about 70%, suggesting that ~ ¾ of variation in the trait is accounted for by genetic variation. MZ twins more likely to share ADHD than DZ twins



Sherman et al 1997, *Am J Psychiatry* (parent+teacher ratings); Langner et al 2013 *PLoS-One (male-female average)*

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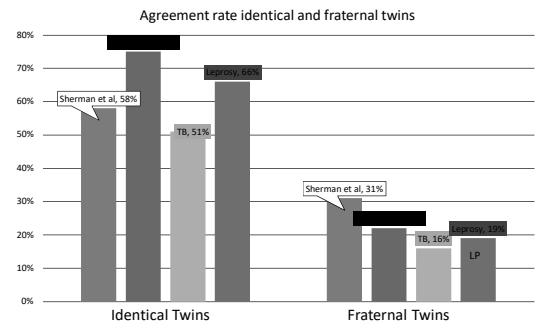
BUT: ADHD does not behave like a single gene metabolic disease

Feature	Single Gene Disorder (PKU, Huntington's)	ADHD
Role of genes	Mostly deterministic	probabilistic
Disease incidence	Rare (< 1/10,000)	Common (>1/100)
Increased sibling risk	Large (~1000x)	Small (~3-10x)

© Joel T Nigg 2016, idea from Depue & Monroe, 1988

AND the picture is not much different for major infectious diseases.



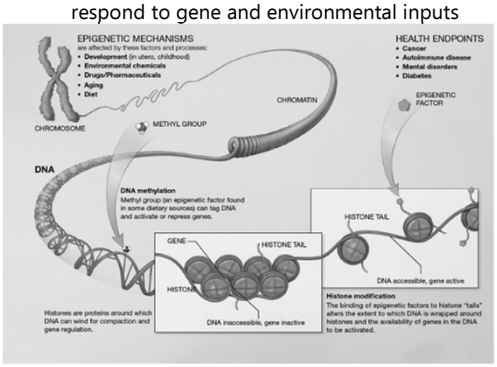
© Joel T Nigg, 2017. TB & Leprosy rates estimated from studies cited in Hill, AVS, 1998; *Ann Rev Immu.; and in* Fine PE,1981, *Int J Lepr Other Mycobact Dis, 49*, 437-454

Proposed view of ADHD as epigenetic

- Does NOT mean "all environmental" and not "2 types"
- ADHD heterogeneous
  - but many routes are potentially GxE or epigenetic.
  - Likely very little "all or none"
- Thus: susceptibility (substantially genetic) + experience (epigenetically mediated effects) = complex syndrome
- With
  - varying manifestations
  - temporal variations,
  - multiple routes to emergence and recovery

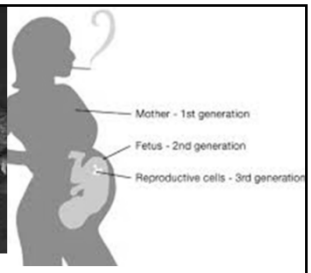
SHORT DETOUR: WHAT IS EPIGENETICS ANYWAY?

What is it? Epigenetic markings change gene activity, respond to gene and environmental inputs



https://commonfund.nih.gov/epigenomics/figure. © NIH

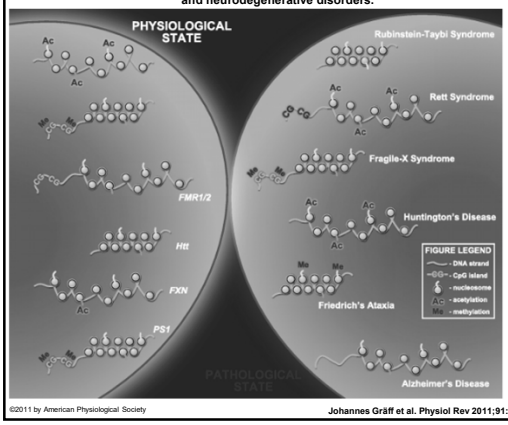
Genetically identical animals with very different phenotype based on epigenetic change caused by feeding different toxicant-diet combination to the mother (R Jirtle et al, Duke University; *Mol Cell Biology* , 23, p. 5293, 2003; © Elsevier Inc.) MCB)



Most events affect only the person exposed, but germ line (transgenerational , 2nd or 3rd generation) effects are known. (Jablonka & Raz 2009, *Quarterly Review of Biology*, 84:131–76; © University of Chicago Press)

Epigenetic Effects based on experiences can, in principle, be as large as genetic effects, although this is unknown in humans

Overview of the best-documented examples of epigenetic deregulation in neurodevelopmental and neurodegenerative disorders.



Johannes Gräff et al. Physiol Rev 2011;91:603-649

ARE ENVIRONMENTAL CORRELATES OF ADHD CAUSAL?

If we accept a susceptibility model of ADHD: Which Environments do we study and how do we do it?

- Sociological Effects
  - Collapse of civilization
  - Too much pharma marketing
  - Performance pressures on children, starting school too young
- Caregiver Problems
  - Over-indulgent or else hostile/intrusive parenting
  - Under-trained or inexperienced teachers
- Developmental and Biological Context
  - Rare events
    - Perinatal problems, teratogens (alcohol, drugs); micro-ischemias
    - Extreme toxicant exposures, extreme neglect (Romanian orphans)

***
  - Common but harmful contexts
    - Modern screen Media
    - Moderate psychosocial stress/distress (esp. prenatal)
    - Poor diet
    - Low grade Toxicant/pollutant exposures (pre-natal, post-natal)

Substantial literature links ADHD to environmental risk factors in development

- Toxicants
  - Lead; PCB's; BPA; Pesticides
- Dietary insults
  - Western high-fat diet during gestation
  - Western diet (additives) in development
- Gestational and perinatal risks
  - Parental stress, BMI, smoking, other exposures
  - Infant distress, birthweight, delivery complications

But are these causal?

- Plausibility (can "low amounts" do harm?)
- rGE and unexamined genetic effects
- Unmeasured confounders

Toddler attention altered by prenatal DHA supplementation (single object free-play session; increasing look time predicts stronger cognitive development later; i.e., high IQ=growing ability to sustain focus) from Columbo et al 2004, Child Development 75, 1254

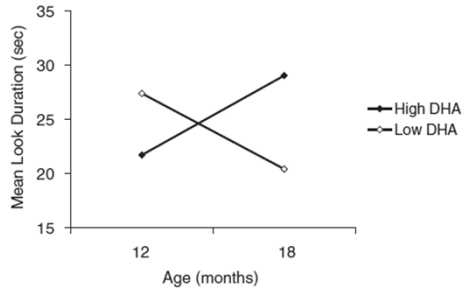
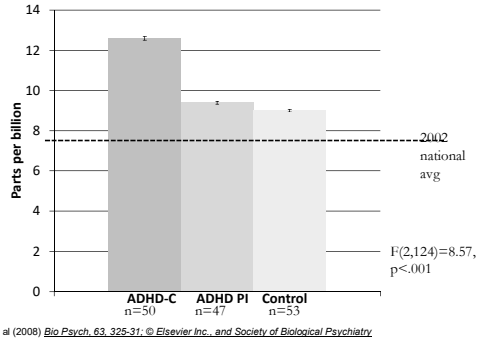
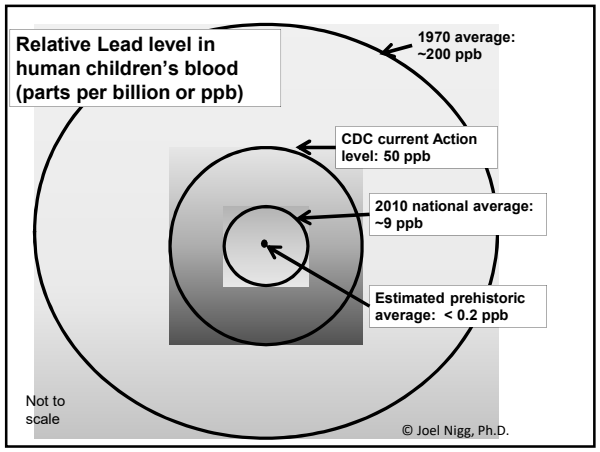


Figure 3. Developmental course of look duration during single-object, free-play sessions at 12 and 18 months as a function of high and low maternal docosahexaenoic acid (DHA) at delivery.

Example: Blood Lead and ADHD 2005-2007



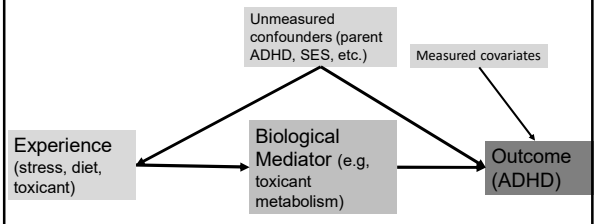
Data from Nigg et al (2008) *Bio Psych, 63, 325-31; © Elsevier Inc., and Society of Biological Psychiatry*



How can we evaluate causality of environmental influences on ADHD in humans when experimental tests are not possible?

- Surrogate pregnancy—(e.g., smoking, Thapar et al)
- Sibling, twin, adoption designs
- Natural stratifications (e.g., Dutch famine; or one city stops vaccinations)
- Mendelian randomization** (focus today)

MENDELIAN RANDOMIZATION LOGIC



Source: Adapted from Lewis et al., 2013, Journal of Child Psychology and Psychiatry, 54, pages 1095-08; © ACAH, JCPP. Slide © Joel Nigg, Ph.D.

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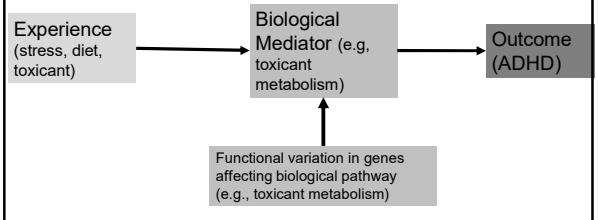

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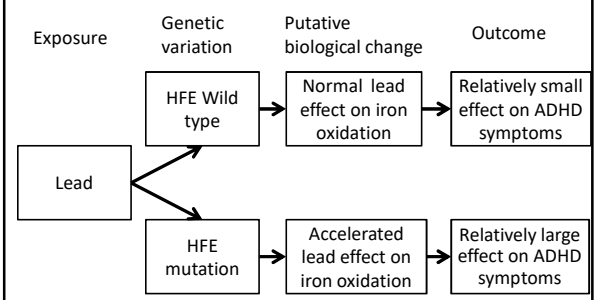
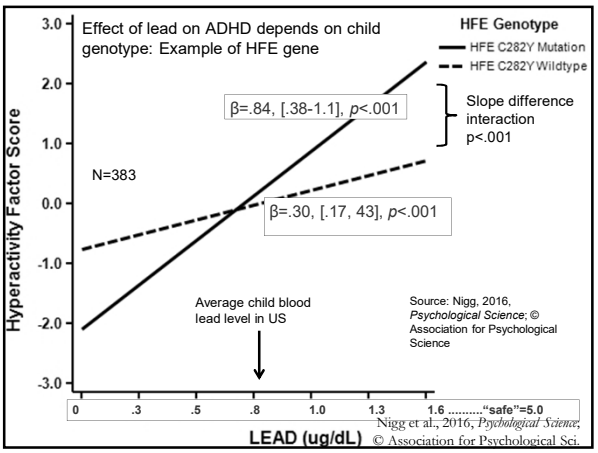


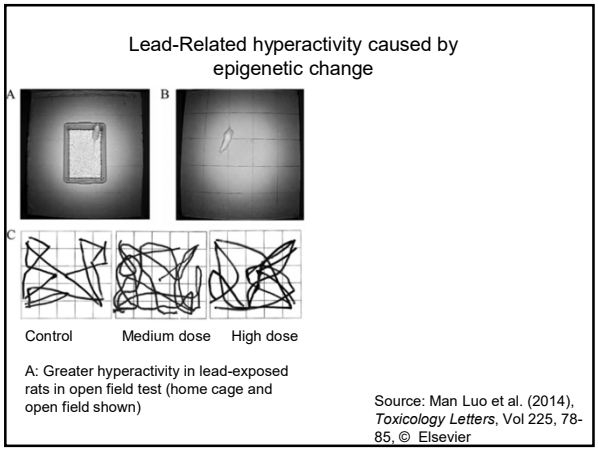
Schematic of hypothesized effects for lead x HFE interplay in ADHD

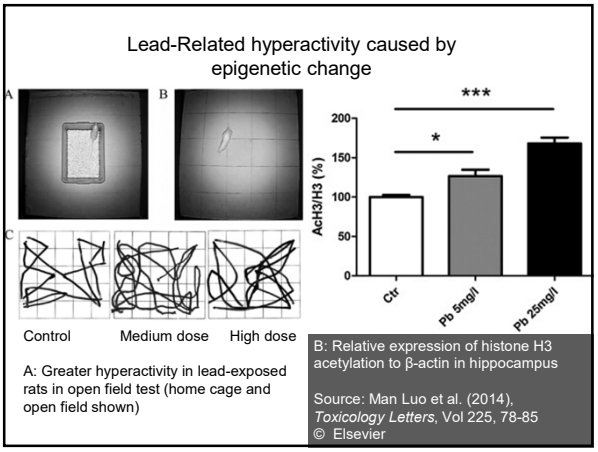
Source: Nigg et al., 2016, *Psychological Science*; © Association for Psychological Science

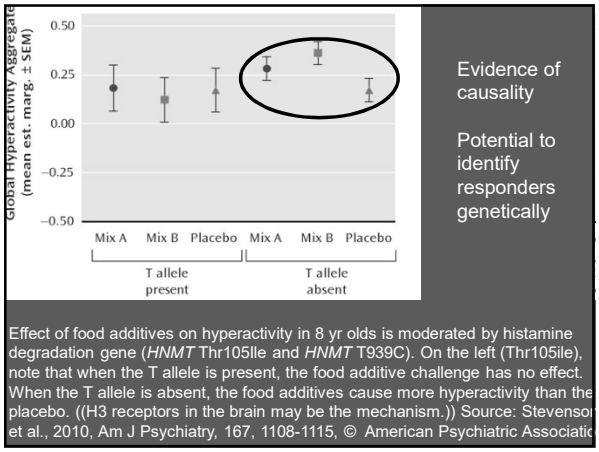
How we proceeded on lead+ADHD

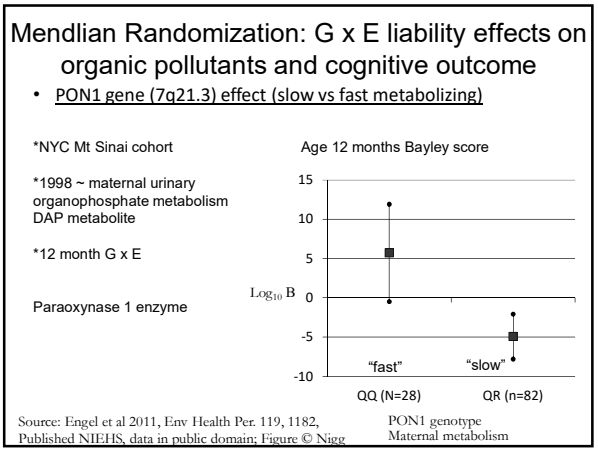
- Replicated the ADHD-low-lead correlationi(n=213)
- Then combined both samples, (Total N=363; ADHD+control)
- Mendelian randomization design
- HFE gene (6p22.2)
  - iron uptake in gut, lead x iron interplay)
- Weakness: Lacked an independent replication
- Strengths of our study
  - ADHD very well characterized
  - Genotype frequencies matched the regional population
  - Control group blood lead levels matched the population
  - No high blood levels (max=3ug/dL)
  - rGE controlled
  - Race/ethnicity, SES controlled











Examples Linking findings in ND: causally informative designs

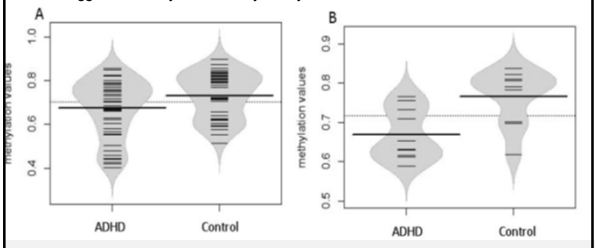
- Lead → ADHD (Nigg et al, 2016)
- Lead → epigenetic change-> RNA brain-> hyperactivity (Luo et al. 2014)
- Prenatal chemical toxicant→ ADHD, IQ, autism (e.g., Engle et al 2011)
- Prenatal omega-3 intake → infant IQ (e.g., Columbo et al 2004)
- Food additives-> ADHD (Stevenson et al 2010)
- Epigenetic mediation (e.g. Skinner et al 2014)
- We should not be uncritical but should consider these linkages carefully

Epigenetic studies in ADHD in humans

- Strategies
  - Population based vs enriched case-control
  - Candidate gene/probe vs MWAS
- Cautions
  - Tissue specificity and inaccessibility
    - Biomarker vs causal pathway
  - Dynamic
  - Multi-causal (genetic, experience, random)
    - But may help find mechanism of gene action

? Epigenetic biomarkers? First methylome-wide epigenetic study of ADHD—one interesting finding

VIPR2 probe **cg 13444538 methylation values of ADHD and non-ADHD boys in a discovery cohort (n=88, panel A, p=.03) and a replication cohort (n=20, panel B, p=.006) showing decreased methylation in ADHD.** Source: Wilmot, Fry, Musser, Mill, & Nigg, J Child Psychol and Psychiatry, 2016



VIPR 2 also linked to psychosis, circadian clock, and brain development, a rodent knockout model confirms link to hyperactivity

Key findings in DNA methylation in ADHD in children

- Van Mil et al J Psych Res 2014: 7 candidate genes examined in cord blood→ ADHD sx at age 6 (CBCL); DRD4, 5HTT.
- Walton et al (2016), altered DNA methylation at birth associated with future ADHD trajectory (AVON study, n=872)
- Barker et al 2017 (Child Dev)(n=671, ALSPAC), cord blood MWAS related to ODD and overlap with ADHD symptoms
- Wilmot et al 2016 (JCPP), n=92 boys case control MWAS, VIPR2 (later confirmed for boys) and MYT1L (confirmed in mixed male-female sample later)

Conclusions

- ADHD hypothesized as at least in part an epigenetic response to widespread low grade insults in genetically susceptible children
- At least some exposure effects appear to have causal link to ADHD
- Genetically informed studies of environment can clarify causal effects
- Initial epigenetic effects in ADHD show promise, although many cautions are in order

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