NEUROEPIGENETICS AND COGNITION: A BRAVE NEW NEURO WORLD

NAME OMMITTED
CMB 250
Tuesday, April 26th
AGENDA

1. Brief Intro to Epigenetics and Neuroepigenetics (what, who, when?)
2. Importance cognitive processes (why?)
3. Technology in current Neuroepigenetic research/ Approach (how?)
4. Future Implications (where?)
5. Sweet Endings
6. References/Questions
WHAT IS EPIGENETICS?

DEFINITION:

• Origin of Definition: 1942 C. H. Waddington: “the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.”

• “Epi”

• Modern Definition: “the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence.”

• However.... Many Epigenetic modifications interfere or assist in silencing and expression of noncoding sequences.... “heritable alterations that are not due to changes in DNA sequence”

• 25 Years, 1990’s ~98% of all the research published in epigenetics was published within the last 15 years
MECHANISMS OF EPIGENETICS

**EPIGENETIC MECHANISMS**
are affected by these factors and processes:
- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

**HEALTH ENDPOINTS**
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

**DNA methylation**
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

**Histone modification**
The binding of epigenetic factors to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
TRANSGENERATIONAL EPIGENETICS: A TALE OF INHERITANCE

• The four basic methods of Transgenerational Epigenetic Inheritance include:

1. Transcriptional loops where mRNA or protein products of a gene encourages transcription of said gene; Example: Wor1 gene in Candida albicans which regulates white/opaque pigmentation

2. Cytoskeletal and environmental structure cues; for example: cytoskeletal structures, cilia and flagella, prions

3. chromatin marks, in which methyl or acetyl groups bind to DNA nucleotides or histones

4. RNA silencing, siRNA, snRNA, RNAi interferes with the transcription of DNA or translation of mRNA.
WHITE/OPAQUE EPIGENETIC REGULATION IN CANDIDA ALBICANS
A MECHANISM OF TRANSGENERATIONAL EPIGENETIC INHERITANCE (GENOMIC IMPRINTING)
WHY IS EPIGENETICS IMPORTANT?
NATURE VS. NURTURE

A better answer to the age old questions

- Influences: learned behavior, neurotoxicology, CNS development, cognition, addiction, and psychopathology, cancer, over-all health, aging, etc.

Influenced by: Diet, Exercise, drugs, toxins, in utero development, surrounding environment, etc.
HOW DOES EPIGENETICS WORK?

• Can modify our progeny via Addition or removal of chemical groups to our DNA, Histone modifications, … etc.
• To list several of the main Epigenetic modifications:
  • stable, long-term epigenetic modifications that involve DNA methylation
  • Short-term modifications involve histone modifications, such as methylation and acetylation
1. Epigenetic tags and chromatin structure
2. DNA Methylation/Demethylation
3. Histone Modifications
4. Non-coding RNA and transcriptional gene silencing
SO IF THAT’S **EPIGENETICS** WHAT IS **NEUROEPIGENETICS**?

- Simply put Neuroepigenetics is epigenetics applied to the CNS.
- Cell differentiation can often be attributed to epigenetic factors (Glia, Motor Neurons, Neurons, Oligodendrocytes, etc.) Cytoskeletal structures/ internal environments.
- *In-utero* development such as imprinting can lead to Cognitive deficits on either side from hypo- to hyper-.
- Drugs, Diet, and exercise.
- Stressful experiences (memory's and PNS responses).
WHAT INFLUENCES NEUROEPIGENETIC MODIFICATION?

• While our epigenome is modified in more ways and in more depth than time allows here the major components of Neuroepigentic modifications can be visualized in *Table 1*.

• *Table 1.* lists a variety of mechanisms behind Neuroepigentic modification these are caused by various stimuli and otherwise environmental factors.
AN EMERGING FIELD COGNITIVE NEUROEPIGENETICS: COGNITION, MENTAL ILLNESS, AND BEYOND.

- Neuroepigenetics is still in its infancy.
- While it's well-known and accepted that epigenetic inheritance and modification plays a vital role in the regulation and expression of our genes as well as our cellular phenotypes. The specificity's and implications of the science is not fully uncovered. Leaving it in an era of trial and error as well as seemingly endless hypothesis of importance or the range of possibilities that can be addressed using this approach.
- Generalizations are mostly true, but given the ambiguity of an emerging field its constantly shifting as new secrets emerge.
- What are all the implications?
- May one day overcome genetics alone to provide a fuller picture of disease, and other genetic modifications/ expression
A BRIEF LIST OF NEUROEPIGENETIC APPLICATIONS

- Explanation for differences in cognitive and otherwise abilities in Identical Twins
- Cancer
- Addiction/Reward system regulation (pharmaceutical, and illicit drugs, gambling, sexual intercourse, etc.)
- Learning and Memory
- Cognition
- Happiness/Depression
- Perception (pain, temperature etc.)
- Neurodegenerative Disease (Parkinson's, Alzheimer's, etc)
- Neurogenesis (cell birth/neuronal plasticity/ metaplasticity (plasticity of plasticity)/ Growth & development)
- Mental Illness/Deficits: ADHD, PTSD, Schizophrenia, Bipolar Disorder, Retts Syndrome, Autism, Fragile X, etc.) (imprinting)

As illustrated in Table 2, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3878295/table/T2/
EPIGENETICS IN COGNITION: WHAT IS COGNITION?

• Cognition is the study of mind and its processes. Cognitive science deals with perception, learning, memory, recognition, linguistics, developmental neurobiology etc.

• Cognitive Neuroepigenetics Works to explain the interaction between ones genes (“nature”) and ones environment (“nurture”).

• As it relates to Perception, Learning, Memory, and All other faucets of Human Cognition.
EPIGENETICS IN COGNITION: EXAMPLES OF EPIGENETIC MODIFICATIONS
COGNITION AND PERCEPTION

• Learning and Memory: Histone Modifications, DNA Methylation, piRNAs, miRNAs.

• Human Cognition - Mental Retardation Syndromes and Cognitive Disorders: DNA Methylation, HAT activator molecule, CREB-binding protein, RNA silencing etc.

• Pain Perception: Histone modifications, HDAC, miRNA, methylation.

• Depression/Suicide: DNA Methylation
• Epigenetics and Pain Perception, Neuropathy and Inflammation:
• ~100 million adults suffer from chronic pain, annually this costs Americans roughly $635 billion
• A 2006 study found that a large majority (over-half of the test sample) report having little to no control over their pain management
• Opioid drugs are often first line in the management of pain (this can lead to epigenetic up/downregulation of dopamine receptors/vesicles and other neurotransmitters, leading to depression, ill-health, and possible addiction)
• epigenetics in pain perception enhance or suppress gene expression without modifying primary DNA coding.
• DNA methylation, histone modifications (namely acetylation, methylation, phosphorylation, and ADP-ribosylation), also expression of microRNAs (miRNAs) make up the Epigenetic Mechanisms behind Pain perception and related ailments (addiction, depression, suicide etc).
EPIGENETICS IN COGNITION: CONTINUED (PERCEPTION)
EPIGENETICS IN COGNITION: CONTINUED (HUMAN COGNITION)

• Learning and Memory: According to J. David Sweatt et al.
• “its ability to regulate gene transcription dynamically in response to neuronal activation supports the consolidation of long-term memory. Furthermore, the persistent and self-propagating nature of these mechanisms, particularly DNA methylation, suggests a molecular mechanism for memory maintenance.”
EPIGENETICS IN COGNITION: CONTINUED (HUMAN COGNITION)
# Technology and Neuroepigenetics: Tools of the Trade

- [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880494/table/T2/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880494/table/T2/)

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>N</th>
<th>Brain region</th>
<th>Method</th>
<th>Results</th>
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<tbody>
<tr>
<td>(Mill et al, 2008)</td>
<td>Schizophrenia, bipolar disorder</td>
<td>105</td>
<td>Frontal cortex</td>
<td>mCpG sensitive restriction digest, CpG promoter array</td>
<td>Approximately 100 CpG islands with altered DNA methylation in disease cohorts. BDNF mCpG levels differ between rs6265–val66met polymorphisms.</td>
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<td>(Zhang et al, 2010a; Gamazon et al, 2012)</td>
<td>Schizophrenia, uni-bipolar depression</td>
<td>164</td>
<td>Cerebellar cortex</td>
<td>DNA bisulfite conversion, Illumina Methylation Bead Chips to probe &gt; 27K CpG</td>
<td>Approximately 3000 SNPs linked to methylation of ~700 CpG in cis and SNPs to 12 CpG in trans. Multiple GWAS-related SNPs are linked to RNA expression and CpG methylation in cis.</td>
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<td>(Shulha et al, 2011)</td>
<td>Autism</td>
<td>32</td>
<td>Frontal cortex</td>
<td>Neuron-specific histone H3K4me3 profiling by fluorescence-activated nuclei sorting (FANS) and deep sequencing (ChiP-seq)</td>
<td>No significant alteration on group level. Approximately, 700 sequences with altered H3K4me3 in variable subsets of cases included ~90 neurodevelopmental risk genes (ASTN2, CACNA1C, CACNA1H, MJD1C, MEF2C, NRCAM, PARK2, RA11, RIMS3, RYR2, SEMASA, and many others).</td>
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TECHNOLOGY AND NEUROEPIGENETICS: TOOLS OF THE TRADE

NIH Common Fund (Roadmap) Epigenomics Program Components
NEUROEPIGENETICS OF THE FUTURE!

• So… What is up and coming in the world of Cognitive Neuroepigenetics?
CONCLUSIONS/SWEET ENDINGS

• Neuroepigenetic traits are caused by modifications of
• Histones via methylation, acetylation, phosphorylation etc.
• PTMod’s of DNA including the above
• RNA Silencing

• Within the next 10-25 years as sequencing tech continues to grow and the secrets of the epigenome are unlocked some mental illness's, disease, cancer, behavioral traits, and beyond may be able to be regulated and controlled by influencing our environmental factors and stimuli.
• Cognitive Neuroepigentrics could have far reaching implications from our very own perceptions to the nature of the human mind, and its developmental neurobiology which may transform how we understand ourselves, disease, and the world around us.
REFERENCES

- Schneider, A. et.al. (2013). Acetyltransferases (HATs) as targets for neurological therapeutics. Neurotherapeutics. 10: 568-588.
- Neuropsychopharmacology Reviews (2013) 38, 183–197; doi:10.1038/npp.2012.78; published online 30 May 2012
THANK YOU!