The Future of Behavioral Science: One Perspective

Merrill
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Who moved the cheese??
Why do we have such a hard time convincing the public, Congress and other scientists about the need for behavioral science?
Everyone has a theory of behavior.....
The science of behavior is the new “rocket science”. It is moving very quickly and is very exciting but disciplines such as psychology and psychiatry must change or they are in danger of becoming obsolete.
One Word

Plasticity
The changing science of behavior

The modern integration of:

Brain/Behavior
Mind/Brain
Nature/Nurture
Genes/Environment
We now understand that our genes specify a general plan with many options. Our brain changes its physical structure through behavior and interactions with the environment. The brain is the substrate of our thoughts and behavior.
Genes: multiple susceptibility alleles each of small effect

Cells: subtle molecular abnormalities

Systems: abnormal information processing

Behavior: complex functional interactions and emergent phenomena
The brain is the substrate of our thoughts and behavior.
Genes guide the general structure of the brain throughout our lives.
The physical structure of our brain changes under the influence of our behavior and the environment.
Neurogenesis in the Adult Human

Source: Eriksson et al., 1999
Physical Activity & Neurogenesis

Source: van Praag et al., 1999
Stress Impairs Neurogenesis

Gould 2000

Dentate Gyrus, Marmoset Monkey

BrdU Labeled Cells/mm³

Control

Stress

* p<.05

Gould 1998

Dentate Gyrus, Adult Rat

BrdU Labeled Cells

Dominant

Subordinate

* p<.05

Gould 2000
Voluntary Exercise leads to increase in the number of BrdU-positive cells 24 hours post-BrdU injection and environmental enrichment leads to no change at this time point.

Olson, AK et al. Hippocampus. 2006;16(3):250-60
The percentage of BrdU-positive cells remaining at 4 weeks

Olson, AK et al. Hippocampus. 2006;16(3):250-60
Prairie Vole  
(Microtus ochrogaster)  
Highly social  
Biparental  
Pair bonds  
Sep. Distress - High

Montane Vole  
(Microtus montanus)  
Asocial  
Minimally Parental  
Promiscuous  
Sep. Distress - Low
Prairie (and Pine) vole microsatellite insert in the V1a receptor promoter

\[\cdots \cdots \text{(GACA)}_8 \cdots \text{(AC)}_4 \cdots \text{(AC)}_4 \cdots \text{(AG)}_5 \cdots \text{(CATA)}_9 \cdots \text{(GA)}_{13} \cdots\]
But the environment and behavior changes gene activity
Epigenetic programming by maternal behavior

Ian C G Weaver¹,², Nadia Cervoni³, Frances A Champagne¹,², Ana C D’Alessio³, Shakti Sharma¹, Jonathan R Seckl⁴, Sergiy Dymov³, Moshe Szyf²,³ & Michael J Meaney¹,²

Here we report that increased pup licking and grooming (LG) and arched-back nursing (ABN) by rat mothers altered the offspring epigenome at a glucocorticoid receptor (GR) gene promoter in the hippocampus. Offspring of mothers that showed high levels of LG and ABN were found to have differences in DNA methylation, as compared to offspring of ‘low-LG-ABN’ mothers. These differences emerged over the first week of life, were reversed with cross-fostering, persisted into adulthood and were associated with altered histone acetylation and transcription factor (NGFI-A) binding to the GR promoter. Central infusion of a histone deacetylase inhibitor removed the group differences in histone acetylation, DNA methylation, NGFI-A binding, GR expression and hypothalamic-pituitary-adrenal (HPA) responses to stress, suggesting a causal relation among epigenomic state, GR expression and the maternal effect on stress responses in the offspring. Thus we show that an epigenomic state of a gene can be established through behavioral programming, and it is potentially reversible.
Maternal licking and grooming changes the brain permanently

Source: Meaney and Szyf, Trends in Neuroscience, September 2005
By changing gene activity permanently

Source: Meaney and Szyf, Trends in Neuroscience, September 2005
Environmental enrichment changes the brain also

Source: Bredy et al. European Journal of Neuroscience, July 2004
Understanding Mental Illness
Relation Between Maternal Remission Status and Change in Child's Specific Diagnoses (Baseline to 3 Months)

Medial Prefrontal cortex can modulate fear expression via projections to the amygdala.

mPFC

Amygdala

Fear
Evidence in Humans: PTSD Patients Fail to Show mPFC Activation When Exposed to Traumatic Reminders
Non-PTSD
PTSD
Depression
Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Avshalom Caspi,¹,² Karen Sugden,¹ Terrie E. Moffitt,¹,²* Alan Taylor,¹ Ian W. Craig,¹ HonaLee Harrington,² Joseph McClay,¹ Jonathan Mill,¹ Judy Martin,³ Antony Braithwaite,⁴ Richie Poulton³

Science, 302: 386-388, 2003
Genotype Interacts with Stress to Increase Risk of Depression

Among those who had 4+ episodes of life stress; 33% of “s” genotype developed MDD vs. 17% of those with “l” type genotype.
Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma


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Critical Role of Cg25 in Depression: Converging Evidence

SSRI

Placebo

TMS

ECT

Mayberg

George

Nobler

Dep: ↓volume; ↓glia

nl: SERT s/s < l/l

Structural Changes

Drevets, Ongur, Rajkowska

Pezawas
Cg25WM DBS Procedure

- Local anaesthesia
- Leksell frame
- MRI Targeting

- Microelectrode mapping
- Insertion bilateral electrodes (Medtronic 3387)
- Turn on the devices/program (acute, chronic stimulation)
Acute Intra-operative Stimulation Effects
Contact and voltage specific

Spontaneous Self-Reports
• Sense of intense calm, quiet, relief
• Dissipation of visceral symptoms
• Resolution of the ‘pain,’ dread, void, mental heaviness

Followed within 15-20 seconds by
• ↑ interest, energy, personal connectedness
• ↑ attention, motor speed, spontaneous speech
• Δ visual perception; colors, clarity, brightness, details
• Δ PANAS: ↑ positive; ↓ negative scores

Adverse Effects
No autonomic, motor, overt mood changes
Mental slowness at top contacts near cc.

Awareness of a sudden shift from an all-consuming internal focus
to the realization there are other things around to do...
## Change in Depression Scores

<table>
<thead>
<tr>
<th></th>
<th>Wk 0</th>
<th>Wk 1</th>
<th>Wk 2</th>
<th>Wk 12</th>
<th>Wk 26</th>
</tr>
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<tbody>
<tr>
<td><strong>Mean HAMD17 Scores</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Men (n=8)</td>
<td>24.0</td>
<td>14.0</td>
<td>16.0</td>
<td>13.5</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>+2.8</td>
<td>+4.2</td>
<td>+6.95</td>
<td>+2.1</td>
<td>+3.96</td>
</tr>
<tr>
<td>Women (n=4)</td>
<td>26.8</td>
<td>14.5</td>
<td>17.7</td>
<td>13.8</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>+2.6</td>
<td>+7.8</td>
<td>+8.5</td>
<td>+9.4</td>
<td>+5.1</td>
</tr>
</tbody>
</table>

*All time points significant different from Wk 0; p<0.05; 8/12 R (66%)
No significant differences between Men and Women

7 pts at 1 yr: 5/7 R (71%) 3/7 Remitters (42%)
Patient’s Perception of DBS Effects

Patient 5: 2 months of Stimulation

“the most fundamental change that I can see, is that it isn’t like something has been added—no, something has been taken away. That heavy sinking vortex feelings was always there in some form or another. And now it is gone. (acute primary change at target?)

It is as if instead of being in the grand canyon, you are now up on a ledge, no longer in a pit. You look around, and you know it is still 800 feet to where I want to be, but you are not in a hole anymore. Now it comes down to you. (new learning, plasticity, rehabilitation?)"
Ketamine

- Non-barbiturate, rapid-acting disassociate anesthetic
- Non-competitive NMDA receptor antagonist
  - Slow blocking kinetics of open channel
- Psychotomimetic properties (5-20%)
- Abused as “club drug”
- Studied in: schizophrenia, cognition, alcoholism, chronic pain syndrome, and neuroprotection
Response Rates to Ketamine in a Double-Blind Placebo Crossover Trial in Patients with Treatment-Resistant Major Depression (N=18)

Response: 50% decrease in HAMD from baseline

Summary: Modulation of Common ‘System’ Treatment-Specific Effects

Emotion-cognition integration

- mF9/10
- aCg24
- oF11

Attention-cognition

- PF9
- P40
- pCg

Hippocampus

- bg
- thal

Mood state

- Emotion-cognition integration

Vegetative-circadian

- Cg25
- a-ins
- am
- hth
- bs

Drug

CBT

CBT inverse

SRI only

CBT only
We need a science of behavior which is an integrative and inclusive science
Change happens
Change is happening faster
Change creates opportunity