The Neuroscience of Mind Body Medicine

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Disclosure

• Johns Hopkins University Press—royalties for:
  
  * Compassion and Healing in Medicine and Society. On the Nature and Uses of Attachment Solutions to Separation Challenges. 2011*
Hippocrates (c. 460-370 BCE) and Auden (1907-1973 CE) and the Importance of Integrative Health

“Natural forces within us are the true healers of disease. It is far more important to know what person the disease has, than what disease, the person has.”

“‘Healing’,/Papa would tell me,/‘is not a science,/but the intuitive art/of wooing Nature’.”

W.H. Auden, The Art of Healing
Objectives

- State integrative medicine hypotheses
- Introduce an evolutionary neurobiological approach to understanding integrative health and mind body medicine
- Review neuroscience of the stress response, the relaxation response and resilience
- Establish a heuristic mind body medicine equation that can aid us in our clinical and our public health missions
- Propose new neuroscientific strategies for a field of resilience medicine
- Consider implications for public health in the 21st century
Integrative Medicine Hypotheses

1. The environment is biology and mind/body is a unity

2. Psychosocial stress leads to cellular oxidative stress and loss of mitochondrial reserve capacity

3. Cellular oxidative stress leads to disease vulnerability
Stress

- Challenge-Stimulus-Hyperarousal, state with physiological, behavioral, psychological adaptations required of the organism
- General Adaptation Syndrome: mesolimbic-PVN of hypothalamus- (Hans Selye 1950s)
- Inflammatory Stress Response: “neurogenic neuroinflammation”
  Infection-unrelated inflammatory changes in the microglia of the mediobasal hypothalamus $\rightarrow$ activates NF-kB $\rightarrow$ metabolic syndrome (Zhang et al, Nature, 2013)
  Chronic social isolation stress $\rightarrow$ activates NF-kB in rat PFC (Zlatkovic and Filipovic, 2013)
Stress and Performance

• Yerkes Dodson Curve

• When stress exceeds resiliency.

• Burn-out and “compassion fatigue”: Alzheimer’s caregivers and Burn Unit caregivers.

• When stress cannot be metabolized by “allostatic” brain mechanisms, health and performance will suffer.

• External and Internal stress
Fig. 2. Motivation and reward are mediated through the mesocortical-mesolimbic dopamine circuitry with cell bodies in the midbrain tegmentum, axons flowing in the medial forebrain bundle and terminal zones in the amygdala/hippocampus, nucleus accumbens, anterior cingulate/medial orbitofrontal cortex and prefrontal cortex. Memory of the pleasure of wellness and the pain of illness are accessible to this circuitry through hippocampal mechanisms. Belief affects mesocortical-mesolimbic appraisal of an experience leaving one stressed or relaxed. Belief in a placebo can elicit the relaxation response of remembered wellness with salutary effects on the stress response and immune response systems.
Neurogenic Neuroinflammation
Xanthos and Sandkuhler, 2014

Figure 1 | Triggers, actions and outcomes of neuroinflammation. Neuroinflammation can be triggered by 'classical' factors (infection, autoimmunity or toxins) but also by factors that lead to enhanced neuronal activity (including noxious stimuli, psychological stress and epileptic seizures). Immune cells, vascular cells and neurons promote various independent as well as interacting responses (indicated by plus signs). These can be homeostatic, leading to adaptation, or dysfunctional and/or neurotoxic, leading to pathology. Anti-inflammatory mechanisms may be triggered in parallel and serve to terminate neuroinflammation and reduce pathological outcomes (indicated by minus signs). Treatments and interventions may be targeted at various levels to inhibit the triggers and neuroinflammatory processes, or to promote the resolution of inflammation.
Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. Gastroenterology. 2013 Jan;144(1):36-49
Arnsten, 2009
Nat Rev Neurosci
Jovanovic and Ressler, 2010
Benno Roozendaal, Bruce S. McEwen & Sumantra Chattarji
*Nature Reviews Neuroscience* 10, 423-433 (June 2009)
Why Brain Evolution?

• Niko Tinbergen (1963): 4 distinct questions when examining any biological or psychological phenomenon; always involve mechanism and ontology; function and evolution:
  • How does it work? (mechanism, “proximate”)
  • How did it develop? (developmental, “proximate”)
  • What is it for? (mechanism, “ultimate”)
  • How did it evolve? (developmental, “ultimate”)

The Triune Brain in Evolution
Role in Paleocerebral Functions

For
Greg Fricchione
with best wishes for
his studies on the most painful
mammalian condition—
Separation!

From
Paul MacLean
Primordial Intelligence
(Serebriakoff, 1987)

- Sense the environment
- Analyze incoming data
- Effect a motor response: to mobilize or immobilize, to approach or avoid
- Every living organism can be described as a sensory-motor analyzer-effector.
Figure 4.1. *E. coli* Sensory-Motor Analyzer-Effecter. The organism has receptors in the plasma membrane for food molecules such as amino acids. These receptors (four types shown here) pass signal messengers to the internal analyzing machinery, which effects a motor response of approach by causing the flagella to braid up. When negative stimuli such as cytokines are sensed by surface receptors, the analyzer-effector output is modulated.
Figure 7.1. Tetrapod Evolutionary Cladogram. The ancestral amniote tetrapod line had an anapsid skull with no temporal bone openings, only the orbit and nares. The synapsid line, with one temporal opening, diverged from the stem amniote line about 10 million years ahead of the diapsid line, with its two temporal bone openings (my = millions of years ago).
Figure 1. The proposed organization of the neocortex of an early mammal based on a cladistic analysis of the cortex of extant mammals and proportions of neocortex reflected in the endocasts of the skulls of early mammals. Neocortex was small relative to olfactory (piriform) cortex together with the olfactory bulb. Areas of neocortex included primary somatosensory area S1 flanked by rostral (RS) and caudal (CS) somatosensory fields and a second somatosensory area, S2. A taste or gustatory area (g) may have been present. Auditory cortex (Aud) included one (A1) or two primary areas and possibly secondary areas. Visual cortex included a primary area (V1), a secondary area (V2), a temporal visual field (T), and prostriata. Frontal cortex included orbital frontal (OF) and medial frontal (MF) areas but no motor cortex. Cortex of the medial wall of the cerebral hemisphere included granular (RSg) and agranular (RSa) insular (SI), orbital (SOr), and polar (SOP) divisions of insular cortex. From figure, the prominent
Brain Evolution
“The picture’s pretty bleak, gentlemen. ... The world’s climates are changing, the mammals are taking over, and we all have a brain about the size of a walnut.”
Figure 7.5. The Limbic System and Its Connections. Adapted from H. T. Ballantine et al., 1967, p. 491. Used with permission.

Abbreviations: AMYG, amygdala; AT, anterior thalamus; ATR, anterior thalamic radiations; CC, corpus callosum; CG, central gray; DB, diagonal band of Broca; G, nucleus of Gudden; HAB, habenula; HPT, habenulo-interpeduncular tract (fasciculus retroflexus of Meynert); HYP, hypothalamus; INS, insula; IP, interpeduncular nucleus; LMA, limbic midbrain area of Nauta (includes ventral tegmentum); LOT, lateral olfactory striae; MB, mammillary body; MFB, medial forebrain bundle; MTT, mammillo-thalamic tract (Vicq D'Azys' tract); OB, olfactory bulb; PIT, pituitary; SCR, subcallosal radiations; SM, stria medullaris; ST, stria terminalis; UB, uncinate bundle. Areas 8 and 9, dorsolateral prefrontal cortex; area 10, frontopolar cortex; areas 24 and 25, anterior cingulate cortex; and area 29, cingulate cortex.
REPTILIAN EVOLUTION...

Amoebagator  Alligator  Litigator

You get into a car accident, you call me.
• Survival in the ancestral world was contingent upon successful negotiation of a hostile microbial environment which ultimately contributed to a genetically-based inflammatory bias.
The Evolutionary Sources of Stress: The Conflict of Biases

- Individual Selection/Self Preservation: Attachment to food and metabolic energy sources. (All vertebrates)
- Individual Selection/Species Preservation: Attachment to sexual objects. (All vertebrates that sexually reproduce)
- Individual and Group Selection: Attachment to social objects led to a survival advantage. (All mammals and birds)
- Inflammatory bias (communicable diseases) and Social Attachment bias (non-communicable diseases) can wind up in conflict. The Ebola example.
4. Memory of the Future
In the new situation, the PFC makes possible effortless or strategic retrieval of important memories of the past optimizing appraisal of the "what" and "where" of attachment providing for the ability to plan based on memory of the future.

3. a Mammalian Behavioral Triad
- maternal nurturance
- separation cry
- play

b Avoidance of painful separation (visceral, somatic, emotional)
Approach to pleasurable attachment
c memory of the past links the evocative emotional memory of the limbic system with the retrievable declarative memory of hippocampus-association cortices.

1. To Food
   (self-preservation)
   <--> amygdala

2. To Sexual Mate
   (species-preservation)
   <--> septum
Oh, crap! Was that TODAY?
Thought Experiment

- Mammals developed a **selection bias** that involved parental and **social attachment**.
- Humans have evolved to seek **secure attachment** and are hardwired for this attachment solution to produce a biological, healing effect. As Bowlby pointed out, “**man’s environment of evolutionary adaptedness is one of secure base attachment.**” (Bowlby 1973, p. 143; Bowlby 1982, p. 50)
- Resultant solace reduces distress-related downstream negative effects (**allostatic loading**) on our organ systems and promotes health.
- mPFC areas are sculpted by early bonds through epigenetic mechanisms.
- Key in healthy child development-- CDC Adverse Childhood Events (Felletti, Anda, 1998) and **Hardwired to Connect** (2003).
Attachment Neurobiology

- **Spindle cells** (VENS) are specialized to integrate cognitive inputs with emotional overtones, overcoming the **challenge of separation** of cognitive information produced by cortical regions from emotional information produced by the limbic system.

- **ACC** as paralimbic cortex perfectly positioned between limbic system and neocortex to perform this role. Spindle cells specialized for this **attachment solution** function, once they came online, would confer extraordinary prowess in synthesizing cognition and emotion.

- The **ACC-DLPFC–area 10** connections foster the development of self-control and social insight. The **ACC** contributes the cognitive-emotional synthetic analysis required to respond to changing circumstances. **Area 10** provides the ability to plan future adaptive responses based on retrieved memories from the individual’s past experiences.

- **DLPFC** and “**memory of the future**” (Ingvar, 1985) or “**constructive episode simulation**” (Schacter, Addis and Buckner, 2008): in league with MTLMS.

- **Affiliative Neuropeptides**: oxytocin
Allostasis
Sterling and Ayer 1988; McEwen 1998

• “Maintaining stability (‘homeostasis’) through change”
• Capacity to adapt or constantly change thereby modifying physiological parameters in order to adjust to ever shifting environmental conditions.
• At the cellular level, maintenance of healthy mitochondrial reserve capacity.
• The brain does this…

Allostatic Loading

• Wear and tear the body experiences due to repeated cycles of allostasis maintenance. The concept of metabolic energy imbalance.
• Accumulated effects on body of allostatic stress response, as well as inefficient turning on and shutting off.
Allostatic Load

- Cumulative measure of physiological dysregulations over multiple systems; a composite score becomes possible. An AL score is computed as the total number of biomarkers for which participant values fall into high-risk biomarker quartiles.
- 10 markers predictive of functional decline in elderly including:
  
  **12 hour overnight urinary excretion of:**
  
  Cortisol
  Norepinephrine
  and Epinephrine
  
  As well as:
  
  Serum DHEA-S
  Average systolic BP
  Average diastolic BP
  Waist to hip circumference ratio or BMI
  Serum HDL
  Cholesterol to HDL ratio
  Hemoglobin A1C

(HRV is also important as a reflection of sympathetic vs. parasympathetic tone)
Inflammatory Response ↔ Brain Response

- Bi-directionality—Blalock
- Monocyte activation (macrophage hypothesis)
- NF-kB: potential molecular bridge between psychosocial stress and organ pathologies (Bierhaus et al, 2003, 2004) PBMC NF-kB activated by psychosocial stress (15 min Trier Social Stress Test).
- HTN, obesity, IR/DM, LDL (metabolic syndrome) activate pro-inflammatory transcription factor NF-kB as do oxidative stress, cytokines, growth factors, angiotensin II, and advanced glycation end-products (AGEs).
- NCDs (CAD, DM, ESRD etc) are associated with metabolic syndrome and elevated allostatic loading; also have higher levels of depression and anxiety as allostatic load disorders and may be more susceptible to psychosocial stress.
- Chronically activated NF-kB states may then be exacerbated by repeated or perpetuated stress states.
Figure 1. Midsagittal View of the Brain, Showing the Pathways by Which the Brain Monitors Circulating Hormones through the Circumventricular Organs.

Shaded areas indicate the circumventricular organs, specialized areas along the cerebral ventricular surface that have no blood–brain barrier, and their neural connections. Circulating hormones (solid arrows) enter the circumventricular organs and act on neurons, which in turn send into the brain axons (dashed arrows) that regulate physiologic functions related to those that the hormones control systemically. Angiotensin II levels are monitored by neurons in the subfornical organ that project into the hypothalamus to control blood pressure and drinking behavior. Choleystokinin is monitored by neurons in the area postrema that project into the parabrachial nucleus and ventrolateral medulla and ultimately the hypothalamus to control gastrointestinal function and feeding. Circulating cytokines are monitored by neurons in or near the organum vasculosum of the laminae terminals that are thought to control the febrile response through projections to sites in the hypothalamus and the brain stem. The median eminence, pineal gland, and pituitary gland are also without a blood–brain barrier and are sites for the secretion of hormones from the central nervous system into the circulation.
Resilience

• The ability to rebound or bounce back from adversity
• The capacity to maintain stability in the face of mental and physical challenges to well being
• “Success is the ability to go from one failure to another with no loss of enthusiasm”---Winston Churchill
Resilience: Neural Mechanisms

• **Definition:** good adjustment across different domains in the face of significant adversity. (Luthar, Cicchetti and Becker, 2000) Capacity of a dynamic system to withstand challenges to its stability, viability or development. (Masten, 2012) This will be reflected in better energy dynamics—reducing expenditure/building reserve.

• [a] **Fear Responsiveness:** effective behaviors despite fear (Charney 2004)

• [b] **Adaptive Social Behavior:** altruism, bonding and teamwork (Charney 2004)

• [c] **Reward and Motivation:** hedonia, optimism, learned optimism, meaning (Charney 2004)

• **Molecular adaptations** within the mesolimbic brain reward circuitry (MFB) and Stress Systems are associated with vulnerability and resiliency (Krishnan et al, 2007) ---BDNF; 5-HTTLPR; CRF/NPY; DHEA/cort and NPY/NE
Human Resilience

Mind Body Medicine Equation

Stress

\[ \text{Resiliency Factors} \]
- relaxation response
- mindfulness
- social support/pro-sociality
- cognitive skills
- positive psychology
- spiritual connectedness
- exercise
- nutrition
- sleep hygiene
- healthy habits

= Allostatic Load

\[ \text{Vulnerability to Illness} \]
Mitochondrial Resilience

Mitochondrial stress (oxidative)
+ Genetic vulnerability

____________________________ = propensity to illness

Mitochondrial resiliency
+ Genetic endowment

e.g.,
Evolutionary Resilience

Separation Threats
-------------------------------- = Propensity to Illness
Attachment Solutions

The Mammalian Behavioral Triad: separation cry, maternal nurturance and play. (MacLean, 1990)
Adverse Childhood Events and Toxic Stress

**TABLE 1 Summary of CDC-Kaiser ACE Study Findings (Larkin, Sheilds and Anda, 2012)**

*Outcomes associated with the ACE Score*

**Prevalent diseases:** Ischemic heart disease, cancer, chronic lung disease, skeletal fractures, sexually transmitted diseases, liver disease

**Risk factors for common diseases/poor health:** Smoking, alcohol abuse, promiscuity, obesity, illicit drug use, injection drug use, multiple somatic symptoms, poor self-rated health, high perceived risk of AIDS

**Mental health:** Depressive disorders, anxiety, hallucinations, panic reactions, sleep disturbances, memory disturbances, poor anger control

**Sexual and reproductive health:** Early age at first intercourse, sexual dissatisfaction, teen pregnancy, unintended pregnancy, teen paternity, fetal death

**General health and social problems:** High perceived stress, headaches, impaired job performance, relationship problems, marriage to an alcoholic, risk of perpetrating or being a victim of domestic violence, premature mortality in family members

*Problems from the longitudinal follow-up of the study cohort*

**Prescribed medications:** Total prescriptions, prescribed multiple classes of drugs, psychotropics, bronchodilators

**Diseases:** Chronic obstructive pulmonary, autoimmune, lung cancer

**Mortality:** Premature mortality, lung cancer

*Note. A complete bibliography of ACE Study publications listed by topic area is available at http://www.cdc.gov/ace/*.
Does child abuse and neglect predict allostatic load.

Using prospective cohort design, children with documented abuse and neglect matched with non-maltreated children and followed up into adulthood.

Allostatic load assessed with nine physical health indicators.

Child abuse and neglect predicted allostatic load, controlling for age, sex, and race.

Direct effect of child abuse and neglect persisted despite introduction of potential mediators in adolescence and social support and risky lifestyle in middle adulthood.
Maltreated children more likely to have unstable social support across the life span, compared to matched controls.

Social support across life span partially mediated relationship between child maltreatment and allostatic load in adulthood.

These findings have implications for interventions to prevent negative consequences of ACEs.
Attachment, Disease and Illness Behavior
(adapted from Maunder and Hunter, 2001)

Insecure attachment

↑ Perceived Stress

↓ Social modulation of stress

↑ Use of external regulators of stress/mood

Maladaptive use of protective factors

Allostatic Loading

Disease risk factors
- substance abuse
- eating behavior
- risky sexual behavior

Help-seeking
- Social support
- Poor adherence
- Symptom attention

↑ Healthcare utilization

Disease
Stress and visceral pain: focusing on irritable bowel syndrome

Fukudo S.

Fig. 4. Interception pathway. Signals from the gastrointestinal tract ascend the fine parasympathetic afferent fibers and/or fine sympathetic afferent fibers. Parasympathetic afferent signals via the nucleus tractus solitarius and sympathetic afferent signals via the lamina I pass through the posterior ventral medial nucleus (VMpo) or basal ventral medial nucleus (VMb) in the thalamus. These signals are processed in the insula and form the basis of interception. From Mayer et al. [49], with permission.
Right ventral prefrontal cortex (RVPFC) activation associated with (b) physical pain regulation.

Figure I. Right ventral prefrontal cortex (RVPFC) activation associated with (a) social pain regulation

Eisenberger NI, Lieberman MD. *Why rejection hurts: a common neural alarm system for physical and social pain.*

*Trends Cogn Sci.* 2004 Jul;8(7):294-300
# Resilience and Illness

<table>
<thead>
<tr>
<th>Study</th>
<th>Observations</th>
<th>Outcomes</th>
<th>Sample Size</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1992 JAMA</td>
<td>Living alone after MI</td>
<td>c/w↑ risk of recurrent cardiac event at six months</td>
<td>1234 (M, W) age 25-75</td>
<td>Post-MI</td>
</tr>
<tr>
<td>Horsten 2000 Eur Heart J</td>
<td>Lack of social integration plus → 2 depressive symptoms</td>
<td>c/w↑ risk of recurrent cardiac events at 5 years</td>
<td>292 women</td>
<td>Post cardiac event admission</td>
</tr>
<tr>
<td>Ruberman 1984 NEJM</td>
<td>Social isolation Life stress Social isolation + Life stress</td>
<td>c/w ↑ mortality at 36 mos c/w ↑ mortality at 36 mos c/w↑↑↑ mortality at 36 mos</td>
<td>2320 men</td>
<td>Post-MI</td>
</tr>
</tbody>
</table>
Stress Resilience and Physical Fitness and Heart Disease
(Bergh et al, 2015, *Heart*)

• 237,980 Swedish men; 1952-1956
• F/U period: 1987-2010
• Low (51,866), medium (129,806), high (56,308) stress resilience and CHD incidence rates/1000 person-years: 2.61→1.97→1.59
• Higher physical fitness lowered CHD risk but this was attenuated in those with low stress resilience.
• Example of the Mind Body Equation.
Benson Henry Institute (BHI)
Stress Management And Resilience Training
Relaxation Response Resiliency Program (3RP)
(Park et al 2013)

• Individual Integrative Medicine Consultation
• Group: 2 hrs /wk x 8 weeks with booster sessions
• Cardiac Wellness and Rehab: CMS research

• Groups consist of:
  - Relaxation Response
  - Cognitive Behavioral Therapy
  - Social Support and Pro-social Behavior
  - Positive Psychology
  - Belief and Conscious Positive Expectation-Spirituality
  - Exercise and Nutrition and Sleep Hygiene
Relaxation Response

• Self induced stimulus

• **Break train of everyday thought**

• Integrated physiological mechanisms are entrained when a subject engages in a repetitive mental or physical activity and passively ignores distracting thoughts.

• **Vehicles:** meditation including MBSR, prayer, yoga, Tai Chi/Qigong, autogenic training

• **Physiological changes:** ↓O2 consumption, ↓HR, ↓arterial BP, ↓Resp rate c/w ↓metabolism. Preliminary finding also of ↑exhaled NO; RR can change gene expression in counter stress direction in oxidative metabolism, apoptosis, regulation of Ia-Bk/NF-kB (Dusek et al, 2008)
Relaxation Response
(Henry and Stephens, 1977)

• Classically exhibited by the nursing mother.
• Practiced in a religious context, prayer and meditation.
• Muscles relax, breathing is quiet, a contemplative mental attitude.
• In contradistinction to the fight-flight of defense or the state of being cornered.
Mindfulness

• Non-judgmental attention to experiences in present moment to achieve self-awareness and transcendence in everyday life (Kabat-Zinn, 1994) (Vago and Silbersweig, 2012)
• Start with **Focused Attention** (empty mind of everyday thinking to decrease mental proliferation and focus on a single point, e.g, breath, word, phrase, prayer) to elicit **relaxation response**.
• Move to **Insight/Open Monitoring** (no object of focus but receptive in nonjudgmental way to all physical and mental phenomena that arise).
• Can then add **ethical value qualities** (loving-kindness, compassion, forgiveness) OR can do **visual imagery** and add hypnotic suggestion for analgesia for example.
• Achieving relaxation response promotes the physiological and somatic markers of secure attachment.
Meditation and Attachment

- State of relaxation a/w somatic markers reminiscent of a secure attachment physiological profile. (Fricchione, 2011)
- Heightened PNS tone and reduced SNS tone (lower BP and HR); increased heart rate variability (HRV); and reduced oxygen consumption.
- Relaxed meditative state → oceanic feeling of connection in present reminiscent of attunement between the mother-child dyad.
- PNS predominance reflected in lower HR and BP, decreased GSR, increased belly respiratory amplitude, decreased chest respiratory rate and increased high-frequency HRV. (Tang et al, 2009) (Craigmyle, 2013)
- Increasing HRV reflected higher levels of Zen meditation experience. (Peressutti et al, 2010)
Meditation and Attachment

- PNS predominance is reported in relation to attachment and childhood adversity.
- Children with h/o neglect and insecure attachment showed greater sympathetic reactivity and less vagal regulation; reflected in HRV decreases on separation and increases on reattachment than did children with ordered, secure attachment. (Oosterman et al, 2010)
- Reflection of attunement-misattunement-reattunement process; mothers show significant vagal withdrawal during the separation challenge in the Strange Situation test while infants, particularly those with insecure attachment styles, also showed vagal withdrawal.
- Mothers and infants, especially those with insecure attachment, also showed elevated salivary alpha-amylase suggesting increased allostatic loading during the separations. (Hill-Soderlund et al, 2008)
Loving Kindness Meditation

• The following excerpt comes from one of the original teachings of loving-kindness practice.

   Even as a mother protects with her life
   Her child, her only child,
   So with a boundless heart
   Should one cherish all living beings

   (Karaniya metta sutta, 1.8)
Resilience

RR, CBT, Social Support, Positive Psychology, Belief and Conscious Positive Expectation

Reward Motivation, Decreased Fear Responsiveness
Adaptive Social Behavior/Altruistic Love
(Charney, 2004)

Resilience
"I'm learning how to relax, doctor — but I want to relax better and faster! I want to be on the cutting edge of relaxation!"
BHI Studies

• Neuroimaging—Lazar
• Functional Genomics
• Clinical Populations
• Healthcare Utilization

The right BA 9/10 superior frontal and middle gyri and sulci and right anterior insula are significantly thicker in meditators versus age, gender and education matched controls.
Brain regions associated with attention, interoception and sensory processing were thicker in meditation participants than matched controls, including the prefrontal cortex and right anterior insula.

Magnitude of affective response c/w height of response at its peak. Duration is time from the onset of response to return to baseline. Equanimity response involves a rapid recovery function (solid line), in contrast to one that is either low in magnitude (“blunted,” dotted line) or prolonged (“perseverative”, dotted) line).
Right amygdala blood oxygenation level-dependent (BOLD) contrast signal time series during reaction to negative self-beliefs and breath-focused attention in social phobics (SP) at both pre- and post mindfulness-based stress reduction (MBSR)

- **Self-networks and neurocognitive systems supporting S-ART.** This working model represents task positive (self-specifying: EPS and EES), task negative (NS), and integrative fronto-parietal control networks. It also represents individual components of attentional systems and prosociality network purported to be modulated by mindfulness.

- The substrates for component mechanisms of mindfulness within S-ART are depicted.
Mindfulness practice is associated with neuroplastic changes in the ACC, insula, temporo-parietal junction, fronto-limbic network, and default mode network structures.

General intelligence factor (cognition, decision-making, imagination, ToM) on a single positive-negative axis may be related to brain connectivity in this same network. Smith et al, 2015 Nat Neurosci.
Transcriptome: PBMCs and Brain

• The *transcriptome* : genes expressed at a given time. Study of transcriptomics, also referred to as expression profiling, looks at expression level of mRNAs in a given cell population.

• PBMC gene expression moderately c/w gene expression levels in other tissues including brain. (Sullivan et al, 2006; Rollins et al 2010; Kohane and Valtchinov 2012)

• Possible proxy phenomenon to identify promising PBMC biomarkers for neuropsychiatric disorders including PTSD. (Woelk et al, 2011)
Transcriptomic Methods

- RNA $\rightarrow$ reverse transcriptase + DNA polymerase $\rightarrow$ cDNA $\rightarrow$ fragmentation $\rightarrow$ cDNA fragment library $\rightarrow$ high throughput sequencer $\rightarrow$ sequencer output $\rightarrow$ base caller $\rightarrow$ read by short read aligner $\rightarrow$ RNA sequence analysis methods $\rightarrow$ expression levels
Relaxation Response Induces Temporal Transcriptome Changes in Energy Metabolism, Insulin Secretion and Inflammatory Pathways

Manoj K. Bhasin, Jeffery A. Dusek, Bei-Hung Chang, Marie G. Joseph, John W. Denninger, Gregory L. Fricchione, Herbert Benson, Towia A. Libermann

PLoS One, May 2013
Genomic Signature of Chronic Stress

Miller et al, 2008

- Transcriptional control pathways modified by chronic stress.
- Looked at 11 caregivers for brain Ca patients vs. 10 controls and did monocyte GEP.
- Monocytes showed decreased expression of transcripts for GC response elements but increased expression of transcripts for response elements for NF-kB.
- Reflects functional resistance to GCs + immunoactivation via elaboration of pro-inflammatory pathways.
Replications of Transcriptome Analysis Results with Mind Body Approaches

- Decreased activity of NF-κB family transcription factors and increased activity of the GC receptor as potential mediators of CBSM treatment-induced transcriptional alterations in early-stage breast cancer patients. (Antoni et al, 2011 Biol Psychiatry)

- Yogic meditation intervention may reverse pattern of increased NF-κB-related transcription of pro-inflammatory cytokines in healthy individuals confronting a significant life stressor. (Black et al, 2013. Psychoneuroendocrinology)

- In family caregivers of brain cancer patients with chronic stress, there is deactivation of GC response elements and increased activation of NF-kB gene. Suggests that stress leads to functional GC receptor resistance to GC in monocytes that leads to pro-inflammatory transcription control pathways. (Miller et al, 2008; Biol Psychiatry)
PTSD and The Brain

- **PTSD**: anxiety disorder after trauma. May relate to increased amygdala attention to threat cues. (El Khoury-Malhame, 2011)
- Extinction of fear responses to threat cues is impaired in PTSD: dysfunctional activation of fear extinction brain regions, i.e., BLA, hippocampus, ventromedial prefrontal cortex (vmPFC), and dorsal anterior cingulate cortex (dACC). (Milad, 2009)
- PTSD: structural and functional compromise of the ACC, a/w impairment of ability to regulate the amygdala.
- ACC volume is smaller a/w combat-related PTSD, broadly consistent with ACC hypofunctionality. (Woodward 2006)
- Val158Met genotype moderates the effect of PTSD-related processes on right ACC volume. (Schulz-Heik, 2011)
- PTSD is associated with decreased activity in the DLPFC. (Reichert, 2006) (Cohen, 2004)
- Glatt et al, 2013 Am J Med Gen: pre-trauma PBMC GEP (particularly activation of cell mediated immune genes) differed between trauma exposed Marines who developed PTSD and those who did not. See also Ursano group’s brain GEP study.
Neurocircuitry model of PTSD

Cognitive Regulation

+/-

dlPFC

vmPFC

Hippocampus

Context

Thalamic

Sensory input (CS-US)

“Alarm System”

dACC

Insula

Amygdala

Threat response coordination

Cognitive Regulation

+/-

+/-

+/-

Neurocircuitry model of PTSD

Sensory input (CS-US)
Human Well-Being
(Fredrickson et al, 2013)

- PBMC transcriptome analysis from subjects with hedonic (pleasurable needs met) vs. eudaimonic (meaningful other-regarding purpose) well-being
- **Stress-related conserved transcriptional response to adversity pattern:** increased expression of genes associated with NF-kB induced pro-inflammatory cytokines.
- Those with eudaimonic well being have deactivation of their NF-kB and activation of anti-viral IRF gene sets.
- Relaxation Response Resiliency Training counter-regulates the stress-related conserved transcriptional response to adversity pattern and enhances well-being by recreating the physiological and somatic markers of **secure attachment.**
Cumulative Mortality Rates for BHI Group and Controls: Tertiary Prevention

(Shepard et al, 2009)
Resiliency Training Effect on Resource Utilization

• Retrospective database analysis using RPDR

• Intervention (n=4452):
  – All patients receiving Relaxation Response Training through the MGH Benson-Henry Institute from 1/12/2006 to 7/1/2014

• Control (n=13149):
  – Matched by age, ethnicity, gender

• Limitations: retrospective study; data categories are not specifically designed for clinical studies; patients could leave the network; artificial pre and post phase for control group.
## Average Utilization by Site of Service

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<thead>
<tr>
<th>Site of Service</th>
<th>Observations (n)</th>
<th>Pre</th>
<th>Post</th>
<th>P Value</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Medicine</td>
<td>INT: 380</td>
<td>2.3</td>
<td>1.18</td>
<td>0.008</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>CTL: 580</td>
<td>1.79</td>
<td>2.24</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Specialty Care</td>
<td>INT: 4818</td>
<td>19.77</td>
<td>10.13</td>
<td>&lt;.0001</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>CTL: 10092</td>
<td>3.63</td>
<td>3.96</td>
<td>0.002</td>
<td>↑</td>
</tr>
<tr>
<td>Urgent Care</td>
<td>INT: 2344</td>
<td>2.05</td>
<td>0.99</td>
<td>&lt;.0001</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>CTL: 1254</td>
<td>0.79</td>
<td>0.81</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Emergency Department</td>
<td>INT: 2888</td>
<td>3.61</td>
<td>1.67</td>
<td>&lt;.0001</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>CTL: 4858</td>
<td>1.65</td>
<td>1.41</td>
<td>0.004</td>
<td>↓</td>
</tr>
<tr>
<td>Hospital Admission</td>
<td>INT: 380</td>
<td>2.3</td>
<td>1.18</td>
<td>0.008</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>CTL: 580</td>
<td>1.79</td>
<td>2.24</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

*Average encounters/patient/year*
Mind Body Medicine Results

Astin and colleagues (2003): strong to moderate evidence of efficacy in:

- Cardiovascular disease (Dusseldorp, et al, 1996) (Linden et al, 1994),
- Hypertension (Jacob et al., 1991) (Linden, and Chambers, 1994),
- Insomnia (Morin et al, 1994) (Wang) et al, 2005),
- Low back pain (van Tulder et al, 2000),
- Headache (Haddock et al. 1997) (Holroyd and Penzien, 1990) (Sierpina et al, 2007),
- Arthritis self-care (Lorig and Holman, 1993) (Superio-Cabuslay et al, 1996),
- Surgical outcomes (Dreher, 1998) (Johnston and Vogele, 1993)
- Cancer treatment tolerance (Redd, 2001).
Mind Body Medicine Results

Pelletier (2004): strong evidence for:
• Acute pain (Seers and Carroll, 2004) and fibromyalgia (Hadhazy et al, 2000)

Current RCTs indicate positive efficacy:
• Allergies (Watkins, 1994),
• Asthma (Castes et al, 1999) (McQuaid, and Nassau, 1999) (Smyth et al, 1999),
• Dermatological disorders (Kabat-Zinn, et al 1999),
• Post-stroke rehabilitation (Moreland et al, 1998),
• Peptic ulcer (Levenstein, et al, 1999),
• Pregnancy outcomes (Scott et al, 1999),
• Chronic obstructive pulmonary disease (Devine and Pearcy, 1996),
• Tinnitus (Andersson and Lyttkens, 1999)
Health Promotion and Illness Prevention

By improving resiliency and by preventing stress related mental distress, physical and mental health benefits may occur-- Primary, Secondary and Tertiary Prevention
Non-Communicable Diseases (NCDs)

- Medical Diseases that are non-infectious and non-transmissible among people
- Often chronic, of long duration and of slow progression
- Contribute to more rapid death and years lost to disability
- High burden worldwide
- Risk factors vary across regions
- Ethnic variations in susceptibility of disease

Figure 1. NCDs constituted more than 36M deaths (60%) worldwide* in 2005 according to the WHO; 80% of deaths occurred in LMICs
Non-Communicable Diseases

• Stress related chronic non-communicable diseases (NCDs) (cardiovascular diseases, chronic respiratory diseases, diabetes, arthritis and neuropsychiatric diseases) continue to plague primary care practitioners → can only slow progression of the disease; enormous suffering and contributing to the ballooning of health care costs.

• NCDs represent the most important global health challenge of the 21st century in terms of disease burden and mortality. (Narayan, Ali and Koplan, 2010)
Stress Related NCDs and Immunoactivation


- Psycho-physiological disorders are caused by or exacerbated by stress/allostatic loading.
- Allostatic loading affects the IRS which then may uncover disease vulnerabilities in susceptible individuals.
- NCDs (CAD, DM, ESRD etc) are associated with elevated allostatic loading; also have higher levels of depression and anxiety as allostatic load disorders and may be more susceptible to psychosocial stress.
- Chronically activated NF-kB states may then be exacerbated by repeated or perpetuated stress states.
- Immunoactivation may be the foundation for much of human disease.
Figure: Biomarkers and clinical staging in psychiatry

Nieman and McGorry, Lancet 2015
A Cautionary Tale: the U.S.

- Health spending in the U.S., where there is an EBM business model, reached an estimated $2.8 trillion in 2012.
- National health spending averaged $8,680 per person in 2011.
- Health care accounted for 17.9 percent of the gross domestic product in both 2010 and 2011.
- Despite the share of the economy consumed by health care, U.S. health outcomes continue to lag behind other industrialized nations and performs below par in such measures as rates of infant mortality, life expectancy, and premature and preventable deaths.
- A forgotten factor: whole person integrated care.
- Accountable Care Organizations? Medical Homes?
IOM Committee Report
“Better Care at Lower Costs”

- Recommendation 1: The digital infrastructure.
- Recommendation 2: The data utility.
- Recommendation 3: Clinical decision support.
- Recommendation 4: Patient-centered care. Involve patients and families in decisions regarding health and health care, tailored to fit their preferences.
- Recommendation 5: Community links. Promote community-clinical partnerships and services aimed at managing and improving health at the community level.
- Recommendation 6: Care continuity. Improve coordination and communication within and across organizations.
- Recommendation 7: Optimized operations. Continuously improve health care operations to reduce waste, streamline care delivery, and focus on activities that improve patient health.
- Recommendation 8: Financial incentives.
- Recommendation 9: Performance transparency.
- Recommendation 10: Broad leadership.
Integrated Systems Care
Bousquet et al. *Genome Medicine* 2011, 3:43; http://genomemedicine.com/content/3/7/43
Compounding Interest of NCDs and Mental Illness: Depression and Cardiovascular Disease

(Hare et al, Eur Heart J, 2013)
Biobehavioral Influences on Cancer Progression
(Costanzo et al, 2011, Immunology and Allergy Clin NA)
"I did it! I did it! I found a substitute for quality!"
“Systems awareness and systems design are important for health professionals, but they are not enough. They are enabling mechanisms only. It is the ethical dimensions of individuals that are essential to a system’s success. Ultimately, the secret of quality is love. You have to love your patient, you have to love your profession... If you have love, you can then work backward to monitor and improve the system.”

Avedis Donabedian, MD, MPH (1919-2000)

December 2014
IHI 25th National Forum Keynote Address - Donald M. Berwick, MD
Health Care ➔ Health Creation: “We need to become students of well-being”
https://www.youtube.com/watch?v=r5Tbikk44jY&feature=youtu.be
“Yeah, but good luck getting it peer reviewed”
The Digestive System

Lobbyists start salivating.

Health Care Reform

Interest groups pulverize issue

Congressional hearings churn contents

Financial contributions produce digestive juices

Political opponents produce bile and invertece

25 miles of committee hearings complete final compromise

You can guess the outcome

The system continues to run smoothly?
*Peabody (1927): “The good physician knows his patients through and through and his knowledge is bought dearly. Time, sympathy and understanding must be lavishly dispensed but the reward is to be found in the personal bond, which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient.”

*Churchill (c1940): “Charity in the broad spiritual sense, that is, our desire to relieve suffering, is the most prized possession of medicine.”

  - Cognitive: influence and convince → 50% with improved health outcomes (BP, pain)
  - Emotional: warm, empathic style with relief of anxiety and fear + cognitive → 75% with improved health outcomes
Whole Person Integrated Care as Attachment Solution

• Scientific competence AND compassionate, loving care, using language and behavior and self-care education our patients inherently understand as a result of humans’ evolutionary heritage fulfills the need to find attachment solutions to the problem of separation threat.

• “The solution is to discover a way to reconnect doctor to patient through a bridge of common understanding and shared ways of knowing about disease. We need nothing less than a new philosophy of medical knowledge” (R. Horton, Health Wars, 2003, p. 58).

• Perhaps modern medicine would do well to base its patient care approach on our evolutionary heritage—the need to find attachment solutions that provide solace and healing.

• Whole Person Integrated Care strives to do this...
Figure 1.
Interventions by developmental phase
Neuroscience, Yes
Figure 1.1: “The Doctor” by Sir Samuel Luke Fildes. 1891.