Health of mind captured: a brain trained to body talk

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The brain and its body: beyond the experience of the outside

• „Holistic” approach
• Homeostasis
• Interoception

Disturbance in *mental illness* (i.e., stress- and trauma related disorders with depression and anxiety):

SOCIAL ENVIRONMENT – BRAIN - BODY
Posttraumatic stress disorder (PTSD):
- Intense anxiety
- Nightmares and flashbacks
- Social isolation
- Depression
- Impaired learning and memory

Comorbidity and overlap with Major depressive disorder (MDD)

Modified after Koolhaas JM et al., 2011
**Traditional Chinese Medicine** (14-11 cent. BC, Shang dynasty)
- Brain functions are distributed among the five *zhang*-organs
- Brain diseases: systemic diseases

**Ayurveda** (Hindu Medicine, 5000 BC)
- Brain: sensation, movements, rational processes
- Mind controls body: meditation as a *treatment*

*Western systematization and reductionism*  
*Eastern holism*

*Modified after Sakatani, 2007*
**Plato** (c. 427-347 BC):
- Tripartite theory of soul: logical, spirited, and appetitive
- Brain: separated from other ‘mind-system’ by the neck

**Aristotle** (384-322 BC):
- Soul is not a separate substance of which the body is made
- Brain: to cool the blood (and sleep)

*Descartes, Kant, Huxley* and others
Enlightenment’s *rationalism* and *empiricism*

**THOUGHTS CAN CONTROL EMOTIONS AND YOU CAN LEARN HOW TO CHANGE IT**
The fundamental basis of *Aaron Beck’s* (1976) concept:
**COGNITIVE-BEHAVIORAL THERAPY (CBT)**
Thoughts cannot change everything: past memories of the unacceptable (the legacy of depressive and traumatic realism)

MINDFULNESS-BASED APPROACH
(Jon Kabat-Zin, 1978)

- Based on Buddhist tradition Vipassanā
- Remember (e.g., a trauma, major life events)
- Non-judgmental and non-elaborative reflection
- Focus on thoughts, feelings, and emotions from a mental distance in the present
- Contemplate, be open, and accept

CBT & „Mindfulness“ is an evidence-based treatment of major depression and related conditions according to the NICE (National Institute for Health and Care Excellence) guidelines (CG90, 2009; updated: October 2012)
An unexpected moment in the meeting of East and West: The historical role of Transylvania (Romania and Hungary)

Ram Mohan Roy (1774-1833)

Unitarian Church of Transylvania (since 1565)

The Church of Székelyderzs (ca. 1300-1340)
Fundamental questions

• What is the effect of environmental intervention (e.g., CBT & Mindfulness) on the brain and cognition?
• How is it related to changes in body?
• What is the specific role of inflammation and the microbiota – gut - brain axis?
• Is there any translational potential in basic findings?
The human microbiota – gut – brain axis

- 100 trillion bacteria
- Diversity and individual patterns
- Viruses regulating bacteria
- 4 million extra genes
- 100 million neurons (the „second brain”)

Role:
- Neuropsychiatric illness
- Aging
- Metabolic syndrome
- Autoimmune processes/allergy

Modified after Lozupona et al., 2012 and Tillisch & Labus, 2014
CBT and "Mindfulness"

Psychobiotics
Beneficial/Probiotic Microbes
e.g., *Lactobacillus reuteri*

Physical, Physiological, and/or Psychological Stressor Exposure

Circulating cytokines
Anxiety-like behavior

Stressor-Induced Physiological Response
e.g., Glucocorticoids, Catecholamines

Disruption of Homeostatic Interactions Between Host and Microbiota

↑ Susceptibility to mucosal pathogens
↑ Inflammation
↑ Epithelial barrier disruption/Bacterial translocation

*Modified after Bailey, 2014; Hariri and Holmes, 2006; Swidinski A et al., 2007*
Measures of intestinal permeability, stress response, and low-grade inflammation

- **16s RNA**: bacterial ribosome
- **TLR-4** (Toll-Like Receptor-4): detecting bacterial lipopolysaccharide (LPS)
- **IL-6** (Interleukin-6): most abundant circulating cytokine
- **CRP** (C-reactive protein): inflammatory protein produced by the liver
- **FKBP5**: regulator of cortisol receptor
- **NF-κβ**: transcription factor activated by cytokines
- **BioM-10**: a 10-item transcriptomics marker of stress and depression (activated glial cells and lymphocytes)
Toll-Like Receptor 4 (TLR-4) activity in microglia and astroglia

Markers of bacterial translocation and TLR4 activation in individuals with major depression following major life events: the impact of therapeutic intervention

**Bacterial 16s rRNA**

* $p < 0.05$

**TLR-4 and TLR-2 activation in lymphocytes**

- t1 – before CBT
- t2 - after CBT (16 weeks)
- MDD – major depression
- HC – healthy controls

*p < 0.05*
Changes in gene expression in lymphocytes: before vs. after CBT

10-item transcriptomics marker scores

NF-κβ

Genes related to growth factor signaling, cytokines, and glial functions:
MBP, EDG2, FZD3, ATXN1, EDNRB
FGFR1, MAG, PMP22, UGT8, ERBB3

t1 – before CBT
t2 - after CBT (16 weeks)
MDD – major depression
HC – healthy controls
The relationship between symptom changes during CBT and TLR-4/NF-κβ

HAM-D – Hamilton Rating Scale for Depression
The relationship between symptom changes during CBT and BioM10

BUT: negative results for IL-6 and CRP (minor changes during CBT and no correlation with symptom improvement)
Interim summary: increased intestinal permeability, inflammation, and depression

- Evidence of bacterial translocation (16s RNA)

- Primary immune activation (TLR-4)

- Complex changes in leukocyte gene expression

- Effect of psychological intervention (CBT)

Kéri Sz et al. J Affect Disord 2014;164:118.
Figure modified after Tillisch & Labus, 2014
The HPA (hypothalamic – pituitary - adrenal axis) and cortisol: new targets for stress- and trauma-related disorders

Receptors for non-genomic actions, receptor modulators, and cortisol-inducible genes:

- **FKBP5**
- **GPR30**
- **GLIZ**
- **SGK-1**

[Diagram of the HPA axis with receptors and stress pathways]

Modified after Raabe & Spengler, 2013; Fani N et al., 2013; Scharf SH et al., 2012
Changes in brain volume in patients with posttraumatic stress disorder (PTSD): before vs. after CBT

FreeSurfer ROIs (Fischl B et al., 2002)

Hippocampal formation
Amygdala
Medial orbitofrontal cortex (mOFC)

Levy E et al. Biol Psychiatry
2013;74:793.
Indicators of intestinal permeability and cortisol receptor sensitivity in PTSD: before vs. after CBT

Following CBT:
- Decreased intestinal permeability (16s rRNA↓)
- Decreased cortisol receptor sensitivity (FKBP5↑)
- No changes in RPS6K, the peak significant marker of PTSD from Affymetrix® array
- Blood cortisol levels are not conclusive
Three-way correlation among improvements in posttraumatic symptoms, FKBP5, and hippocampal volume changes (post- vs. pre-CBT)

- Better improvement (reduced CAPS scores)
- Increased hippocampal volume
- Higher FKBP5 expression

CAPS – Clinician Administered PTSD Scale

Common impairment in stress- and trauma-related disorders: hippocampus-dependent memory

**Paired – associates learning:** object – place associations

„**Candy box**” task:
- computer-based
- with real persons (social influences on learning)

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**Kéri Sz. Cortex 2014;54:200.**
Interim summary

• Evidence for:
  - increased gut permeability
  - enhanced cortisol sensitivity (low FKBP5)
  - decreased hippocampal volume in PTSD
• CBT: some of these correlated deficits are ameliorated
• Paired-associates learning is boosted, especially in the social context
Is there impaired neuronal plasticity in people experiencing negative life events, showing pronounced low-grade inflammation but have no mental illness?

A method for cognitive training: *games* (2 months, 30 min/day)

**Super Mario®**: spatial navigation, shifting allocentric and egocentric strategies

**Mahjong**: clearing the board by removing all tiles in pairs that are identical, no other tile is lying above, left or right, or partially covering it
Structural changes in the human brain (after vs. before training)

The relationship between right hippocampal volume changes, negative life events, and $\text{NF-}\kappa\beta$
Interim summary

• Popular games induce structural changes in human brain
• Key regions: hippocampus and prefrontal cortex
• People experiencing negative life events show less plasticity
• NF-κβ is one of the key mediators
Limitations of the microbiota - gut – brain - inflammation hypothesis

• Too general mechanism („housekeeping”)
• Non-specificity of TLR and other pattern recognition receptor activation (damage-associated molecular patterns)
• „Inflammation”: part of normal (neuronal) homeostasis
• Causality
• Microbiota diversity and stability
• Methodological issues (e.g., clinically significant signals in „big data” studies, histological confirmation)
Debates, open questions, and future directions

• Key problem: response rate (CBT, antidepressants): 40 – 60%

• „Psychobiotics”, diet & exercise, n3-fatty acids, vitamin D [...]

• New approach 1: genetically modified microbiota

• New approach 2: pharmacological augmentation of CBT

• Factors that affect BioM10, NF-κβ, and FKBP5:
  - Insulin-like growth factor-I (IGF-I)
  - IL-6, IL-10 (microRNA146b)
  - [Oxytocin]
Acknowledgements

- The patients and their therapists
- The lab at National Psychiatric Center:
  Oguz Kelemen
  Csilla Szabó
  Rebeka Maróthi
- Support of University of Haifa’s PTSD team and Emotion, Trauma, and Loss research group
- The National Excellence Program of Hungary supported by the European Union