CONFUSIONE DEL TERMINE "PSICOSOMATICA"

- Malattie psicosomatiche
- Functional Somatic Symptoms (FSS)
- Disturbi di somatizzazione
- Disturbi funzionali
- Medically Unexplained Symptoms (MUS)
- Disturbi somatoformi (DSM-IV)
- Somatic Symptom Disorder (SSD)
- Illness Anxiety Disorder (IAD)
- Ipocondria (DSM-IV)
- Comorbid psychopathology (CL Psychiatry)

**J.C. Heinroth** coined the term "psychosomatic"

**S. Freud**: theory of conversion hysteria

**W. Cannon**: subcortial emotions may activate downstream hypothalamus (to ANS to illness) and upstream brain cortex (symbolic representations)

**J. Papez**: first description of the limbic circuit

**P. McLean**: 'triune brain': emotions are discharged into the body through the limbic system ("body languages") (1949)

**H. Selye**: the stress model (GAS) (1956)

**F. Alexander**: specificity of emotional factors (one conflict = specific disease), the Holy Seven (Chicago, 1950)

**J. Ruesch**: "infantile personality" (developmental arrest" as the "core problem of the psychosomatic patient") (1948)

**J. Cremerius**: first hospital ward of psychosomatic medicine in München (Germany) (1950)

**P. Sifneos & J. Nemiah**: the alexithymia construct (1970)

**G. Engel**: the Biopsychosocial Model (1977)

**French School** (Marty, De M’Uzan)

**7th medical subspecialty** (ABMS)
NESSUNA malattia è psicosomatica

TUTTE le malattie sono psicosomatiche

ALCUNE malattie sono psicosomatiche

Holy Seven
1. Ulcera peptica
2. Rettocolite ulcerosa
3. Asma bronchiale
4. Ipertensione essenziale
5. Iper/Ipotiroidismo
6. Neurodermatiti
7. Artrite reumatoide

ORGANI CO
Condizione clinica in cui è documentabile una lesione d’organo

FUNZIONALE
Condizione clinica in cui è colpita una funzione somatica ma senza evidenza di danno d’organo

DI SEASE
Malattia di cui è nota l’etiologia (virus, deficit genetico, batterio, ecc)
Processo patologico di deviazione da una norma biologica

ILLNESS
Malessere o disturbo non determinato da agente causale
Esperienza totalmente personale e soggettiva della perdita della salute
Somatization is the tendency to experience and communicate psychological distress in the form of physical symptoms and to seek medical help for them. (Lipowski, 1987)

Somatoform disorders – regardless of their somatic and/or psychological etiology – are due to amplification of normally fluctuating levels of bodily preoccupation and concern that reach a level of sustained intensity that causes psychological derailment or social maladaptation. The threshold to pathology is a function both of psychological feedback loops (vicious circles of anxiety and attention) and of family and social dynamics. Whether any individual crosses this threshold would then be a product of temperamental variability, childhood experiences, sociocultural factors, and the structure and function of the health care system. (Kirmayer et al, 1994)

Decades of literature have shown that psychological factors leading to vulnerability to somatization might be present transversally in different personality organizations, medical diseases, and psychopathological disorders.

Hypochondriasis and Health Anxiety share a component of disease phobia but in beliefs in hypochondriasis often take the form of an ego-syntonic overvalued idea which dominates a person’s thinking and behavior.
Mind and brain are made of two discrete substances with accidental overlapping manifestations

DUALISM

I think, therefore I am

René Descartes

COGNITIVE NEUROSCIENCE

DUAL-ASPECT MONISM

I feel, therefore I am

Jaak Panksepp

AFFECTION NEUROSCIENCE

The brain always functions as a whole.

Mind and brain are made of the same substance, they are the two facets of the same neural coin

EMBODIED COGNITION

Il corpo che sono non è limitato al corpo oggettivo ma è una progressiva mentalizzazione, largamente implicita, dei miei stati somatici
Age and blood pressure in secluded order nuns
20-yr follow-up of meditation and no-stressing living

• 144 nuns in a secluded order in Umbria vs 138 HC women living in the surrounding community, followed-up up for 20 years (enrollment 1964-1968)
• No baseline btw-group difference for age, ethnic background, region of birth, familial environment, education, age at menarche, family history of hypertension, BMI, use of cigarette and oral contraceptives, urinary sodium excretion, blood pressure

Expected increase of BP with age only in HC women. Nuns did not show any BP increase with age and none of them had arterial hypertension.

Time slope of BP values increased significantly with age in HC women but in nuns the slope was near zero.

The only difference was lifestyle: nuns lived in habitat with virtually devoid conflict, aggression, competition for money and power, with silence, meditation, isolation from society.

Timio et al, Hypertension 1988, 12: 457-61
Human emotions are “translated” into 5 channels loading on different times:

- **Musculoskeletal system**
- **Neurovegetative system**
- **Epigenetic system**
- **Neuroendocrine system**
- **Immune system**

Connections between the nervous and immune systems:

Il corpo *che sono* non è limitato al mio corpo personale ma è formato anche dalle relazioni affettive interpersonali.

In questo lavoro fMRI seminale su 16 coppie viene mostrato chiaramente per la prima volta che network cerebrali (ACC e Insula) riflettono il vissuto emotivo delle sensazioni di dolore e costituiscono la base neurale della nostra comprensione dei nostri stessi sentimenti e di quelli degli altri.

Singer et al. Science 2004; 303
The first several weeks of this month were entirely microbial.

Only in the last 4 days animals and plants enter the microbe-dominated biosphere (Cambrian explosion: a relatively short span event, occurring approximately 541 million years ago in the Cambrian period, during which most major animal phyla appeared, as indicated by the fossil record.

Only in the last 30 min of the last day do humans appear

Rook et al, Lancet 2017; 390: 521-30
TIMELINE OF HUMAN NEURAL DEVELOPMENT

Conception | Gestation (weeks) | Birth | Adolescence | Adulthood
---|---|---|---|---
0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 0
Neurulation
Neuropoiesis and gliogenesis
Initiation of haematopoiesis
Migration of immune stem cells and expansion of progenitor cells
Colorization of immune cells
1st trimester
2nd trimester
3rd trimester
Neuronal migration
Apoptosis
Synaptogenesis
Myelination
Synaptic pruning

SEROPTONIN IS PRIMARILY FOUND IN ...

5-HT secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it, where it serves as a vasoconstrictor and helps to regulate hemostasis and blood clotting.

Belongs to the class of monoamines, which includes also NE and DA.
Many adaptive processes are regulated by 5-HT: cell differentiation, temperature, blood clotting, digestion, gut movement, mood, electrolyte balance, autonomic activity, neural apoptosis, cerebral blood flow, attention, aggression, mood, reproductive function, mating behavior.

Approximately 90% of the human body’s total serotonin is located in the enterochromaffin cells in the gut, where it is used to regulate intestinal movements.

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Approximately 90% of the human body’s total serotonin is located in the enterochromaffin cells in the gut, where it is used to regulate intestinal movements.
The body has an ambiguous experiential status as subject / object body. We normally oscillate between these two bodily modes in a flexible way. A consistent bodily self can be established by integrating both perspectives in a balanced and consistent way. When failing, this process results in a pathological embodiment (alexithymia).

My body belongs to me in all its parts in a coherent and continuous way: the sensation that I have a body and that I am that body seems self-evident. I am the feeling of the same old boy always there (W. James, 1890).
BASIC EMOTIONAL SYSTEMS

- The underlying circuits are genetically pre-wired and designed to respond unconditionally to stimuli arising from major life-challenging circumstances: the system is not dependent on higher brain functions.

- The circuits organize behavior by activating or inhibiting motor subroutines (and concurrent autonomic-hormonal changes) that have proved adaptive in the face of life-challenging circumstances during the evolutionary history of the species.

- Emotive circuits change the sensitivity of sensory systems relevant for the behavior sequences that have been aroused: electrically induced arousal of the systems leads to more effective cortical processing (Hebb’s Law).

- Neural activity of emotive systems outlasts the precipitating circumstances by sustaining activity for some time beyond the point of stimulation offset.

- Emotive circuits have reciprocal interactions with brain mechanisms that elaborate higher decision-making processes and consciousness.

- The emotional systems are centrally placed to coordinate many higher and lower brain activities, and each emotional system also interacts with many other nearby emotional systems: no emotions without a thought (sometimes vice versa) and without physiological or behavioral consequences (sometimes these latter can regulate the emotional tone via feedback).

7 BASIC EMOTION SYSTEMS

SEEKING (expectancy)

Persistent exploratory inquisitiveness: engenders energetic forward locomotion-approach with the world (predatory aggression = hunt for food).

It plays a dynamic supporting role for all the other emotions.

- When in the service of positive emotions, it engenders a sense of purpose accompanied by feelings of interest ranging up to euphoria.

- With negative emotions, it prompts a frightened animal to find safety.

It’s the only tonic system (always active) whereas the other 6 are phasic (peaks and resolution).

RAGE

Works in contrast to the SEEKING system, propels the body toward offending objects.

It is fundamentally a negative affective state but can become positive when it interacts with cognitive patterns (pursuing hard objectives, experiencing victory over opponents, imposing or subjugating others).

FEAR

Generates a negative affective state from which all animals wish to escape.

- It engenders tension in the body, a trembling immobility at milder levels of arousal, bursting forth into a dynamic flight patterns with chaotic projective movement to get away.

- May inhibit pain: adaptive mechanism allowing injured animals to escape from predators.

- Humans are the most fearful creatures on earth because can create fears for themselves by imagination.
CARE
Generates impulse to envelop loved ones with gentle caresses and tender ministrations thought opioid secretion. Without this system, taking care of young beings would be a burden.
Contrary to Freud’s idea, it is independent of the LUST system in the brain.

LUST
Sexual excitement: prompting toward flirting activities and moving toward an urgent joining of one’s own body with a receptive mate, culminating in the orgasmic experience.
Mediated by testosterone (that activate also the brain neurotransmitter Nitric Oxidase which promotes aggressiveness and social dominance in the RAGE system), vasopressin, OXT

PLAY
Fundamentally based on taking turns reciprocally at assuming dominant and submissive roles.
Enables the young to learn nonsocial physical skills and cooperative relationships.
It activates neural growth factors as BDNF

PANIC / GRIEF
(separation distress)
Generates insistent crying and urgent attempts to reunite with caretakers (usually mothers). If reunion is not achieved, the young being gradually begins to display sorrow and despairing body postures reflecting the brain cascade from panic to persistent depression.
It helps to facilitate positive social bonding.
It is inhibited by endogenous opioids (also in chemical forms), OXT and prolactin

Substantially all of the psychological specializations within the neocortex are learned… At a basic and motivational level, all mammals are more similar than they are different
7 BASIC EMOTION SYSTEMS

Top-Down
- Cognitive regulation
- Conditioned responses

Bottom-Up
- Influence on learning and development of secondary processes
- Influence on ruminations and thoughts

EMOTIONS
(implicit / non-conscious processes)
- Biological component of affect
- Neuro-physiological and motor-expressive domain of response
- Genetic programs
- Mediated by subcortical and limbic structures
- Largely based on non-verbal clues
- Physiological adjustments needed to meet environmental changes (e.g., visceral sensations and body states projected and mapped in the insula)

FEELINGS
(explicit / conscious processes)
- Psychological component of affect
- Subjective, cognitive-experiential domain of response
- Individual schemas and developmental factors
- Mediated by cortical structures
- Largely based on the symbolic function
- Enable past and current emotional experiences to be accessed and used for decision-making and navigation of the social world (e.g., bidirectional correlation btw the HF-HRV and the medial PFC)

IMPLICIT
Things we do without monitoring them on a moment-by-moment basis

EXPLICIT
Situation in which we can put our experiences into words because we are aware of their occurrence

Jaak Panksepp & Lucy Biven, The archaeology of mind, Norton 2012
The CNS continually monitors our interior and exterior environments. Changes in the internal environment (for example, the degree of contraction of visceral muscles, heart rate, levels of glycaemia, and so on) are sensed by the interoceptive system, signaled to sensory regions of the CNS dedicated to body functions and displayed as neural maps of the body (interoceptive maps). Changes in the external environment are perceived via the exteroceptive senses (smell, taste, touch, hearing and sight) and displayed in dedicated sensory regions as neural maps of the external world (exteroceptive maps).

Changes displayed in neural maps may trigger action programs — sets of innate, programmed physiological actions (wired) aimed at addressing the detected changes and thereby maintaining or restoring homeostatic balance. The actions include changes in internal milieu (heart rate, breathing and hormonal secretion), striated muscle (facial expressions and running) and cognition (focusing attention and favoring certain ideas and modes of thinking).

There are two main types of action programs:
- **Drives** are aimed at satisfying basic instinctual needs (hunger, thirst, libido, exploration and play, care of progeny and attachment to mate).
- **Emotions** include disgust, fear, anger, sadness, joy, shame, contempt, pride, compassion and admiration, and they are mostly triggered by the perception or recall of exteroceptive stimuli (although there are exceptions: for example, fear caused by interoceptive stimuli such as cardiac pain or air hunger).

The changes in body state resulting from an action program are in turn sensed by the interoceptive system and mapped in the CNS. Body state changes mapped in interoceptive neural maps may remain non-conscious or may be experienced consciously as ‘feelings’.

Feelings are mental experiences that accompany a change in body state. External changes displayed in the exteroceptive maps of vision or hearing are perceived but largely not felt directly in the sense of feeling we adopt in this text. However, they may lead to feelings indirectly by triggering an action program that causes a change in body state and is subsequently felt.
Il cervello non registra passivamente stimoli interni o esterni ma è un sistema di processazione creativo che costruisce mappe del corpo: feelings are felt because they map the body ... When the brain makes map, it informs itself.

- **proto-self**: organizzazione che consente di differenziare sé da non-sé
- **core self**: fornisce all’organismo il senso di sé in un dato momento e in un dato luogo. E’ la descrizione del film che scorre nel cervello monitorando le variazioni somatiche: You are the music while the music lasts (T.S.Eliot)
- **autobiographical self**: senso elaborato del sé che colloca l’individuo in un punto del proprio tempo storico

- Siamo immersi continuamente in un ambiente di schermi multiplex su cui vengono proiettate le sequenze del movie-in-the-brain composto dai portali d’ingresso (tracks) del SNC (canali sensoriali, senso interno, senso cenestesico, ecc) (changing maps)
- Io sono la processazione sinaptica “in parallelo” (mappe attive simultaneamente) per cui sono la musica mentre dura, il sentimento di quello che accade nel mio corpo mentre vivo una certa esperienza: images in mind are brain’s maps of anything inside our body and around if, concrete as well as abstract, actual or stored in memory
- Le immagini durante l’attacco di panico (sensazioni fisiche, ricordi, pensieri associati) attivano specifici neural emotion-induction sites di cui il paziente (Luca) può anche non essere consapevole (as-if body loop)

Bechara & Damasio, Games and Economic Behavior 2005; 52: 336-372
Brain areas implicated in stress-related disorders

- Hypothalamus
- Amygdala
- Hippocampus

- Episodic memory
- Declarative memory
- Aggression
- Emotional memory
- Working memory
- Fear extinction

- Behavioral function
- Volume
- Activity

100 trilioni di cellule batteriche rispetto a 10 trilioni di cellule umane (rapporto 10:1)

*Peso totale: circa 1.3 kg*

Il 99% della componente genetica di origine batterica; l'uomo possiede quindi due genomi: il primo fisso ed ereditato dai genitori attraverso i cromosomi umani, e l'altro dinamico e acquisito dai batteri che abitano il suo corpo.

Il 20%-60% di essi, a seconda del sito del corpo in cui si trovano, risultano non essere coltivabili all'esterno del loro habitat naturale. Per tale motivo, nel corso del tempo, si è sottostimata la diversità dei microbiota.

**MICROBIOTA**

- Insieme dei micro-organismi che abitano un particolare organo o tessuto corporeo

**COMMENSALI**

- Microorganismi che non arrecano danni o vantaggi all'organismo ospitante

**SIMBIONTI**

- Microorganismi che apportano un certo vantaggio all'organismo che colonizzano e con cui vivono in simbiosi

**PATOGENI**

- Microorganismi che danneggiano l'organismo causando potenziali malattie.

**NUMERI**

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**MICROBIOMA**

- Somma dei geni di tutti i micro-organismi presenti in un determinato ambiente corporeo o extracorporeo
Microbiota

Human beings, like other mammals, live in a co-evolutionary association (ecological symbiosis called 'holobiont') with huge quantities of commensal microorganisms resident on the exposed and internal surfaces of our bodies. The entirety of microorganisms in a particular habitat is termed microbiota. The collective genomes of all the microorganisms in a microbiota are termed microbiome.

Commensal microbiota are 3 million species of bacteria, 100 trillion microorganisms, 1.5 kg as the human brain and microbiome is 100-fold more abundant than human genome.

**Probiotics**: live micro-organisms that are supposed to provide benefit to host

**Prebiotics**: substances that promote the growth of beneficial microbial organisms

Temporally, the human fetal gut is sterile but colonization begins immediately after birth and is affected by route of delivery, maternal transfer, diet, environmental stimuli and antibiotic usage.

By 1 year of age, an idiosyncratic gut microbiome with adult-like signature is stabilized in each infant.

As other ecosystems, bacteria colonize parts of the human body: skin, airway tract, urogenital tract and particularly GI tract.

Major functions in the gut:
- Defense against pathogen colonization by nutrient competition
- Induction of secretory IgA to defending the intestinal epithelial barrier against bacteria's penetration into tissue
- Facilitation on nutrient absorption by metabolizing indigestible compounds
- Guide of the maturation and functionality of the host immune system

**Dysbiosis** (unbalanced composition of microbiome) may cause chronic low-grade inflammation (IBS/IBD at gut sites, cirrhosis at liver site, viral influenza at respiratory airway sites)
IL MICROBIOMA EVOLVE NEL TEMPO...

BAMBINI
Il microbioma infantile appare estremamente variabile, specialmente durante il primo anno di vita, in quanto è legato prevalentemente al tipo di parto e al tipo di alimentazione.

Il microbioma assume uno schema più simile a quello di un adulto quando l’ospite raggiunge i 3 anni di età.

ADULTI
Nell’età adulta il microbioma raggiunge un equilibrio in termini di abbondanza e diversità batterica e non cambia significativamente in condizioni ambientali o di salute stabili: si trova quindi in uno “stato stazionario”.

ANZIANI
Il microbioma dell’anziano è soggetto a profondi rimodellamenti essendo significativamente diverso rispetto a quello degli adulti più giovani, ed essendo meno diversificato e resiliente e può essere più facilmente modulato da fattori ambientali.

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Some of the health conditions that involve our microbes:

- Acne
- Antibiotic-associated diarrhea
- Asthma/allergies
- Autism
- Depression and bipolar disorder
- Schizophrenia
- Autoimmune diseases (eg, multiple sclerosis)
- Cancer
- Neurodegenerative disorders (eg, PD, AD)
- Diabetes
- Eczema
- Gastric ulcers
- Pain
- Hardening of the arteries
- GI disorders (eg, IBD, IBS)
- Malnutrition
- Obesity
DISBIOSI INTESTINALE E PATOLOGIE DEL SNC

I risultati che emergono dagli studi porterebbero ad ipotizzare un collegamento tra la disbiosi intestinale, ossia tra l’alterazione della flora batterica, ed una serie di patologie mentali nelle quali, altrimenti, non si sospetterebbe in alcun modo dell’influenza del microbioma quale una delle possibili cause scatenanti.

DEPRESSIONE

ANSIA

DISTURBO BIPOLARE

SCHIZOFRENIA

AUTISMO

DCA

DOC

ADHD

PATOLOGIE NEURO-DEGENERATIVE

The gut and vaginal microbiome of the mother is altered by diet, drugs, infection, and stress. If birth occurs through vaginal delivery, the maternal vaginal microbiota colonizes the newborn’s gut. If caesarean delivery occurs, the maternal skin microbiome colonizes the infant gut. Early in life, diet, drugs, and stress can also affect the infant microbiota composition.

The microbiota is important for sex-specific microglial maturation, which is responsible for the neuroinflammatory response. The HPA axis not only is influenced by but also can influence the gut microbiota. Normally, it can attenuate the inflammatory response from the microglia. These four hits could affect this axis and affect brain health later in life. There are also other factors during adulthood that can affect brain health and disease (i.e., environment, disease, stress, and sex).

Codagnone et al, Biol Psychiatry 2018; 85: 150-163
Esistono numerosi fattori che possono interferire con il corretto sviluppo del microbioma. Fra questi, il modo di nutrizione e il modo di nascita sono fondamentali. Il modo di nascita può influire sulla composizione del microbiota, mentre il modo di nutrizione può influire sulla diversità e sulla composizione del microbiota intestinale. Inoltre, fattori come l'approvvigionamento di latte materno e l'esposizione a farmaci in gravidanza possono avere un impatto significativo. La dieta materna, in particolare, può influire sulla diversità del microbiota intestinale. Allo stesso modo, stress in gravidanza possono alterare il microbiota intestinale e aumentare la diversità, che favorisce l’omeostasi immunologica rispetto all’infiammazione. Inoltre, la dieta materna ricca in acidi grassi polinsaturi Omega-3 aumenta la diversità del microbiota intestinale e regolano l'attività dell'asse HPA, preservando la composizione del microbiota intestinale da possibili alterazioni legate a stress materno conferendo protezione anche rispetto a stress futuri.
Microbiota: state-of-the art

- The composition of the microbiota changes at puberty, pregnancy, and the menopause.
- Lifestyle changes distort and limit diversity of the microbiota, particularly in the modern diet in high-income countries.
- Obese mothers might transfer inappropriate microbiota to the infant.
- Microbiota modulates insulin sensitivity and metabolism.
- Microbiota influences diurnal rhythms and cyclical variation in activity of metabolic pathways.
- Caesarean deliveries, reduced breastfeeding, and inappropriate hygiene limit transmission of microbiota to baby.
- Abnormal microbiota, or microbiota of diminished biodiversity, is associated with increased risk of chronic inflammatory disorders, including allergies, autoimmunity, and inflammatory bowel disease.

- Intensive antibiotic use in pregnancy or infancy can also disturb the microbiota and is associated with chronic inflammatory conditions, obesity, and metabolic disorders.
- Perinatal exposures to organisms from farms and dogs correlate with reduced risk of allergic disorders and inflammatory bowel disease (homes and cities need redesigning to optimize contact with natural environment?).
- These exposures drive increased levels of regulatory T cells and accelerate maturation of neonatal type 1 T-helper cell response in animals and human beings.
- Environmental organisms do not necessarily colonize; they might also act as data input to the developing immune system of the gut and airways.

Microbiome in early life

- Link btw pregnancy problems, fetal altered neurodevelopment and later psychopathology?
- More micro-organisms in breast-fed infants
- Cleaning baby pacifier by sucking it diminish the infant risk of allergies
- Protective effect of pet (immune tolerance)
- Higher risk exposure to endotoxin in house dust and larger family size

Link btw pregnancy problems, fetal altered neurodevelopment and later psychopathology?

Microbiota agents in Italy

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose</th>
<th>Labeled cell no.</th>
<th>Total CFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>bifidobacteria</td>
<td>1 vial</td>
<td>$2 \times 10^8$</td>
<td>$1.15 \pm 0.50 \times 10^9$</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>1 capsule</td>
<td>$2.4 \times 10^8$</td>
<td>$2.71 \pm 0.30 \times 10^9$</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>1 bottle</td>
<td>$2 \times 10^9$</td>
<td>$6.92 \pm 5.73 \times 10^9$</td>
</tr>
<tr>
<td>Releifor</td>
<td>5 drops</td>
<td>$1 \times 10^9$</td>
<td>$8.72 \pm 1.53 \times 10^9$</td>
</tr>
<tr>
<td>Profile</td>
<td>1 bottle</td>
<td>$5 \times 10^7$</td>
<td>$2.68 \pm 2.4 \times 10^9$</td>
</tr>
<tr>
<td>Docolfor</td>
<td>5 drops</td>
<td>$1.25 \times 10^8$</td>
<td>$2.16 \pm 0.96 \times 10^9$</td>
</tr>
<tr>
<td>Enzepro</td>
<td>1 capsule</td>
<td>$5 \times 10^8$</td>
<td>$9.65 \pm 1.95 \times 10^9$</td>
</tr>
<tr>
<td>Slevefro</td>
<td>1 sachet</td>
<td>$3 \times 10^7$</td>
<td>$3.51 \pm 3.13 \times 10^9$</td>
</tr>
<tr>
<td>Ferolix</td>
<td>1 sachet</td>
<td>$2.97 \times 10^7$</td>
<td>$4.53 \pm 0.47 \times 10^9$</td>
</tr>
</tbody>
</table>

The amount of micro-organisms in those products is not reduced through the intestinal juice up to 2 hours and/or CFU (colony forming units) can multiply above or after an initial decline the initial amount thanks to colonization.

Vecchione et al, Front Medicine 2018; 5; art.59

Human Genome Project (2001)
Human genome: about 25,000 genes
Human epigenome: 50-70+ times esteemed

Epigenetic differences arise during the lifetime of monozygotic twins

Fraga et al, PNAS 2005; 102:10054-9

Differences in DNA methylation and histone acetylation of 80 Spanish MZ twins

The 50-year-old twin pair shows abundant changes in the pattern of DNA methylation (green and red signals) whereas the 3-year-old twins have a very similar distribution of DNA methylation (yellow).

Although twins are epigenetically indistinguishable during the early years of life, older MZ twins exhibited remarkable differences in their DNA methylations and histone acetylation.
Il nucleo di tutte le cellule contiene il codice composto da 4 basi azotate (nucleotidi) la cui disposizione sequenziale codifica il tipo di amminoacidi e poi proteine per la costruzione delle cellule del corpo.

Porzione del DNA che regola le regioni promoter e enhancer per la trascrizione del gene

Porzione che codifica per le proteine

Nucleotidi o unità ripetute di acidi nucleici formati da 3 gruppi (base azotata di T-A-C-G, zucchero, gruppo fosfato)

Codoni iniziano (start codon) e terminano (stop codon) codificano le informazioni per l’inserimento di uno specifico amminoacido per la sintesi proteica

Il processo di trascrizione delle informazioni genetiche (espressione/silenziamento) viene regolato dall’avvolgimento del filamento attorno ad alcune proteine (istoni)

EPI-GENETICA

Alterazione della sequenza genica causata da fattori extra-DNA

<table>
<thead>
<tr>
<th>Accordo Quali tasti?</th>
<th>Quale gene viene attivato (o silenziato)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinamica (intensità sonora) Quanto forte?</td>
<td>Quanto intensa è l’attivazione (polimorfismo)?</td>
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<tr>
<td>Melodia In quale sequenza?</td>
<td>Quando procedere alla variazione della sequenza di informazioni geniche?</td>
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Variazione genetica con prevalenza >1% nella popolazione, determinata da sostituzioni, delezioni o inserzioni di basi nel DNA in regioni sia codificanti che non codificanti

Melodia

In quale sequenza?

Quando procedere alla variazione della sequenza di informazioni geniche?
Whereas the genome concerns the potential genetic information contained in the DNA which informs gene transcription and expression, the epigenome defines which genes of this potential repertoire are actually expressed.

Genes can respond to a dynamic environment and thereby shape phenotypes such that they are acutely advantageous to the individual (as opposed to advantageous on a much longer evolutionary scale).

11 million-dollar grants, 20 projects, 50 investigators (2016)

Extended Evolutionary Synthesis (cross-generational transmission of epigenetic processes): e.g., some fish species in the Atlantic Ocean adapted to survive in marine environments that are 8 times more polluted than the standard lethal dosage in very few generations.

The study of changes in gene function that are heritable but that do not entail a change in DNA sequence: any process that alters gene expression without changing the DNA sequence.

In other words, "epigenetics" refers to the study of heritable changes that occur not because there is an intrinsic change in the genetic material per se, but because there is a change in the pattern of expression of certain genes as a result of processes other than genetic mutation or recombination. Something influences the genetic code from "above" to either shut down or induce the transcription of genetic sequences, giving rise to either biologically overactive or silent processes.
DNA methylation occurs in Cytosines adjacent to Guanines forming the CpG islands (cytosine and guanine are separated by one phosphate group that links any two nucleosides together in DNA). DNA methylation occurring at regions relevant for gene expression (CpG islands) affects availability of specific proteins within the CNS through inhibition of the transcriptional activity (gene silencing).

Histone modification
Remodeling of chromatin, the structure in which the DNA is wrapped up, and involves covalent modifications at the level of histone tails in order to promote an open or closed chromatin structure. Open chromatin associates with the accessibility to transcriptional factors and increased rates of gene expression, whereas closed chromatin structures are linked to inhibited transcription.

miRNA
microRNA is a small non-coding RNA molecule that is thought to maintain or actively changing the transcription of genes in a heritable way.

RNA and DNA are (ribo-)(deoxyribo-)nucleic acids that with proteins and carbohydrates constitute the four major macromolecules essential for all known forms of life.

Like DNA, RNA is assembled as a chain of nucleotides, but unlike DNA it is more often found in nature as a single-strand folded onto itself, rather than a paired double-strand.
HPA axis is sensitive to changes in the early-life environment that associate with DNA methylation of a neuron-specific exon 17 promoter of the glucocorticoid receptor (GR) (NR3C1). Initial findings were published in 2004.

**EARLY-LIFE ADVERSITY (ELA) AND GR GENE METHYLATION**

HPA axis is sensitive to changes in the early-life environment that associate with DNA methylation of a neuron-specific exon 17 promoter of the glucocorticoid receptor (GR) (NR3C1). Initial findings were published in 2004.

Negative early-life social environments were associated with greater exon 17 methylation in the large majority of studies:

- 70% of animal ELA studies (direct brain tissue analysis)
- 90% of human ELA studies (postmortem as well as peripheral blood and saliva)
- 100% of parental stress (mothers with anxiety/depression, pregnancy-related anxiety, violence or war stress during pregnancy)

In studies of gestational stress, a compelling consensus of increased exon 17 methylation in conjunction with stress in early life was shown both at birth (4 studies) and adolescence or adulthood (4 studies).

Social adversity activates stress responses that include signals such as steroid hormones (e.g., glucocorticoids) or cytokines, which act in multiple cell types and might initiate a coordinated remodeling of the epigenome.

This is consistent with the idea that childhood maltreatment sensitizes neural and endocrine responses to stress, thus establishing a vulnerability for mood disorders.

… even though also negative results have been found

(Marzi et al, Am J Psychiatry 2018, in press)
**GxE study: childhood maltreatment, genetics, adult antisocial behavior**

Australian study, N = 1037 (M = 52%)

Individuals assessed at age 3, 5, 7, 9, 11, 13, 15, 18, 21 and 26

Maltreatment (at age 3-11):
- Severe: 8%
- Probable: 28%
- None: 64%

Genotype MAOA, located on the X chromosome. It encodes the MAOA enzyme, which metabolizes neurotransmitters (NE, 5-HT, DA), rendering them inactive. Genetic deficit of MAOA is linked to aggressive behavior in rats and humans.

Composite index of 4 outcomes (at age 26)
1. Conduct Disorder (DSM-IV)
2. Convictions for violent crimes
3. Personality disposition toward violence (psychological testing)
4. Antisocial PD by-proxy

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**Alleles** = alternate forms of DNA sequencing at a specific locus

**Genotype** = combination of alleles at a given locus

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**MALTRATTAMENTO INFANILE E DEPRESSIONE IN ETA’ ADULTA: RUOLO 5-HTTLPR**

Interazione significativa fra genotipo 5-HTTLPR (1 o 2 alleli Short del genotipo), depressione (a 18-26 aa) e maltrattamento (a 3-11 aa)

\(b=-.33, \ SE=.16, z=2.01, p=.05\)
Telomeres are the protein caps at the end of each strand of DNA that protect chromosomes, like the plastic tips at the end of shoelaces. Without the coating, shoelaces become frayed (genome instability when cells undergo repetitive mitotic divisions) until they can no longer do their job, just as without telomeres, DNA strands become damaged and our cells can’t do their job.

Our body cells replenish by copying themselves. This happens constantly throughout our lives. Telomeres get shorter each time a cell copies itself, but the important DNA stays intact. Telomeres are shortened as we age, but telomeres can also be shortened by stress, smoking, obesity, lack of exercise and a poor diet.

In contrast, TL shortening can be counteracted by telomerase, a ribonucleoprotein enzyme that elongates telomeres by adding nucleotides to the end of chromosomes.

When TL shorten to a critical length, the TL ends are unprotected and initiate classic DNA damage responses, which may lead to apoptosis or to genomic instability (CV diseases, cancer, Alzheimer, all-cause-mortality, MDD).

Faster and more stable attrition in early life than adulthood.

TELOMERE LENGTH AND SEVERE SOCIAL DEPRIVATION

Bucharest Early Intervention Program: 136 children (age 6-30 mo), allocated to Foster Care or Care-As-Usual (state institutions). DNA extracted after 4.5 years of FC/CAU

- % time spent in pre-FS/CAU institution inversely associated w/ telomere length, adjusted for confounders (FC vs CAU, sex, ethnicity, age at DNA collection, low birth weight)
- Effect modified by gender
  - % time in institutional care at baseline predicted telomere length in females (A)
  - % time in institutional care at 54 mo predicted telomere length in males (B)
- This result may help to understanding for
  - the lasting negative impact of early adversity across the lifespan (even with ameliorated social environment as in FC)
  - the delayed onset of some negative health consequences of severe stress (the telomere length difference may not be observable until later in life)

Drury et al, Molecular Psychiatry 2011; 17: 719-27
Childhood Attachment and DNAm

226 healthy children: Strange Situation at 36 m and collection of buccal epithelial cells at age 7

- Disorganized attachment significantly associated with PCA Factor 2 (DNAm difference >10% across participants)

First and largest assessment of infant attachment and variation in DNAm.

**Biological embedding of early experience**
Persisting influence of infant attachment on variation in DNAm.

- The variance amount explained by GxE (59%) was 3-fold higher compared to the E model (attachment only = 18%) and G+E model (adding a single nucleotide polymorphism (SNP) to infant attachment = 23%)

Garg et al, Develop Psychopathol 2018, 30: 891-903
## PSYCHOSOCIAL FACTORS

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<td>Chronic adversities</td>
<td>Optimism</td>
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