HEALTH PSYCHOLOGY: BIOPSYCHOLOGICAL INTERACTIONS

Central questions in Health psychology

- How do the mind and the body influence each other?
  -> Biopsychological Interactions: “mechanisms” POP94a, I0T99a
- Which psychological interventions can contribute to somatic health? How?
  *Curative*: Gezondheidspsychologie deel 3: psychologische behandeling van lichamelijke klachten P0Q37a
  *Preventive*: cf Psychologie van Preventie en Gezondheidspromotie P0P87a + Seminarie P0P95a

Aims

- Thorough knowledge and insight into the basic processes of psychological stress. These imply: Homeostatic regulation & the autonomic nervous system, Central integration of stress response, Inhibition of stress responses, Endocrine stress reactions, Psychoneuroimmunology, Genes, stress and behaviour, Individual differences in stress reactivity.
- Knowledge of contemporary research topics regarding health effects of stress, with a special focus on the (presumed) explaining mechanisms. Furthermore, students are able to relate these research topics with the basic processes of psychological stress. The selected topics can change from year to year. Examples are: psychological factors in the progression of cancer, chronic stress and the metabolic syndrome, influence of prenatal stress from mother on child, psychoneuroimmunology and wound healing, medical unexplained complaints, mental representation of pain, psychosocial factors in cardiovascular and respiratory disease.
- Situating and critically evaluating research on effects of stress on health.
- Developing an attitude to consult also scientific literature outside the field of Psychology (e.g., general scientific or medical journals) and to relate these to psychological literature and models.
- Insight into the relevance of research findings for the setup or evaluation of clinical health psychology interventions.
Disciplines

- Psychology → Models on behavior and mental processes (learning, reasoning, perception).
- Neuroscience → How do the brains function?
- Medicine → How does the body function?

Exam

- Written closed book exam.
  Examples of open questions:
  - Explain (1/2 page max): the amygdala and the hippocampus play different roles in the regulation of cortisol.
  - People typically feel relieved when they have talked about their negative emotions. Explain how “verbalizing emotions” can actually contribute to the dampening of negative emotions and which brain regions are involved in this process (1 page max).
  - A journalist working for ‘radio 1’ is contacting you. She is working on a documentary about students becoming sick more often during periods of exams than during other periods. She asks you, being a health psychologist, for an explanation of this phenomenon. (Max 1 page).

Some tips

- Most students need some incubation time for this course, start in time.
- Try first to get the general story before you try to understand the details.
- Try to link different topics and themes.
Class 1: Homeostatic regulation

INTRODUCTION

Homeostatic regulation

- Organism’s ability to keep its internal environment stable, despite changes in the external environment.
  - temperature
  - blood PH
  - oxygen pressure
  - blood glucose

- Central nervous system = interface for interaction with the external environment.
- “Stress” = threat to homeostasis
  - stressor:
    - physical (cold) or psychological (exam, anticipation of pain).
  - compensatory stress response: producing adrenaline for example.

Physical vs. Psychological stress

Psychological stressor
  ↓ Top down
Homeostatic Threat
  ↑ Bottom-up
Physical stressor

Homeostasis

- = a process which maintains the stability of the human body's internal environment in response to changes in external conditions.
- Feedback control: (there has to be a slight deviation from set point before anything changes)
  examples: temperature
  blood pressure
  arterial carbon dioxide pressure (PaCO2) = blood PH
Baroreceptor reflex = control of blood pressure

Explanation: blood pressure ↗ → receptors stretch
              → are more stimulated
              → send more action potentials to brain stem
              → heart rate decreases (↘)
              → total cardiac output remains stable

http://www.youtube.com/watch?v=G2nLL_O_U7w
Blood PH = amount of CO2 in blood (reversed relation)

- Decreased stimulation of the respiratory muscles by the respiratory center results in decreased ventilation, which decreases gas exchange.

- Increased stimulation of the respiratory center results.

- The increase in blood pH (often caused by a decrease in blood CO2) is detected by the central and peripheral chemoreceptors.

- Blood CO2 levels increase, causing a decrease in blood pH.

- The decrease in blood pH (often caused by an increase in blood CO2) is detected by the central and peripheral chemoreceptors.

- Blood CO2 decreases, causing an increase in blood pH.

- The decrease in blood O2 is detected by the peripheral chemoreceptors.

- Blood O2 increases.

- Increased stimulation of the respiratory muscles by the respiratory center results in increased ventilation, which increases gas exchange.

- Feedforward control:
  - perturbations (verstoringen) are being anticipated and corrected before they occur.
  - classical conditioning as a viable mechanism (e.g exercise “hyperpnea”).
  - increases in ventilation and heart rate occur at the onset of physical exercise, even before an increase in PaCO2.
HIERARCHY OF HOMEOSTATIC CONTROLS

A hierarchy of homeostatic controls

Figure 4.1 Schematic of controls over organic function. The diagram indicates that individual organs have self-regulating capacity. This self-regulation is determined by internal reflexes and the actions of autonomic ganglia located in or near them. Local regulation is modulated in turn by descending influences from the autonomic nervous system, the brainstem, the hypothalamus, and higher centers in the central nervous system.
Vital organs and local reflexes = intrinsic control mechanisms

- Organ adapts its functioning in response to slow, local changes.
  Example: Frank Starling mechanism = heart responses to flow demands caused by systemic circulation.

Explanation:
- If returning (venous) blood volume increases, then atrium chambers fill more before each beat.
- More effective filling of ventricles creates more wall stretch → more muscle fiber tension.
- More vigorous (krachtig) contraction on that beat.
- Left ventricle empties more completely → more effective blood flow into aorta.

- When there are rapid changes or organ function needs to be coördinated → endocrine and autonomic inputs.
Autonomic nervous system (ANS)

Sensory nerve cell.
Inside cell: information through electricity.
Between cells: information through chemical reactions (neurotransmitters).

- Viscera: limited awareness and voluntary control → ‘autonomic’
- Negative feedback
- ANS
  - sensory pathways (afferent)
  - motor pathways (efferent)
  - divisions: sympathetic (SNS), parasympathetic (PNS), enteric
  - reciprocal (onderling) regulation of organic function
ANS and endocrine nervous system
- are coordinated by brainstem: direct control of ANS
  hypothalamus: controls endocrine nervous system, coordinates actions from ANS and ENS. Motor areas with survival behaviors.
- communicate with different organs: complex coordination.
- maintain homeostasis by negative feedback loops
  → brainstem and hypothalamus need to receive information
  → commando’s need to be sent back to organs through ANS or ENS
- when external inputs and behavioral responses that need skeletal system
  → higher brain centers

<table>
<thead>
<tr>
<th>ANS and ENS</th>
<th>Skeletal motor system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory and motory nerves do not reach cerebral cortex</td>
<td>Sensory nerves give info to brain about position and movement of limbs. Motory nerves give commando’s through cerebral cortex (we are aware of our body)</td>
</tr>
<tr>
<td>Elaborated responses</td>
<td>Voluntary control of our limbs</td>
</tr>
<tr>
<td>Limited awareness about the state of our vital organs → no control</td>
<td></td>
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</tbody>
</table>
Each division (sympathetic, parasympathetic, enteric) has
- Sensory pathways from organs via ganglia to brainstem (afferent)
- 4 response components:
  - a) **descending autonomic and preganglionic fibers:**
    - originate in hypothalamus and brainstem
    - go to spinal cord, then to ganglia as preganglionic fibers
  - b) **ganglion:**
    collection of cell bodies and their connections. Part of local regulation system/reflexes.
    Primary station for
    - autonomic motor signals from spinal cord
    - sensory messages returning from organs
  - c) **postganglionic fibers:**
    - from ganglia to target organs
    - messages more elaborated than preganglionic fibers (integrated info)
  - d) **neuroeffector junctions:**
    - sensory impulses are translated into motor action in target organ
    - end of postganglionic fiber secrets neurotransmitter into receptor of target tissue
    and the result is motor action.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Pupillary dilation</td>
<td>Pupillary constriction</td>
</tr>
<tr>
<td>Saliva glands</td>
<td>Viscous saliva</td>
<td>Watery saliva</td>
</tr>
<tr>
<td>Lung</td>
<td>Bronchial dilation</td>
<td>Bronchial constriction</td>
</tr>
<tr>
<td>Heart</td>
<td>Increased rate, force</td>
<td>Decreased rate, force</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Constriction</td>
<td>No effect</td>
</tr>
<tr>
<td>Intestines</td>
<td>Decreased secretion</td>
<td>Increased secretion</td>
</tr>
<tr>
<td></td>
<td>and peristals</td>
<td>and peristals</td>
</tr>
<tr>
<td>Bladder</td>
<td>Relaxation</td>
<td>Contraction</td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>Epinephrine secretion</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Parasympathetic postganglionic nerve fibers are closer to or in organs than those of the sympathetic system (close to spinal cord). Preganglionic fibers can move around on the gangliachain before synapsing with postganglionic fibers.
<table>
<thead>
<tr>
<th>Sympathetic nervous system</th>
<th>Parasympathetic nervous system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganglia far from organ (spinal cord)</td>
<td>Ganglia close to organ</td>
</tr>
<tr>
<td>Ganglia connected</td>
<td>Ganglia isolated</td>
</tr>
<tr>
<td>1:10 pre-post</td>
<td>1/3 pre-post</td>
</tr>
<tr>
<td>Fight/flight</td>
<td>Supporting energy conservation, reproduction, digestion</td>
</tr>
</tbody>
</table>
Sympathetic division ANS

- 1:10 pre-vs postganglionic nerves
  - general, broad influence on viscera
  - extensive linkages across widely distributed ganglia
  - closely integrated actions across different organs (‘in sympathy’)

- Neurotransmission:
  - acetylcholine (preganglionic)
  - norepinephrine (postganglionic): smooth muscle cells, cardiac muscles and pace maker: activating function
  - Except:
    (a) sympathetic preganglionic nerves release acetylcholine at adrenal medulla
      → release of catecholamines (nor-/epinephrine) in blood.
    (b) sympathetic nerves release acetylcholine at sweat glands (hands, feet).

- More active during stress: crucial for fight/flight responses

Parasympathetic (vagal) division ANS

- Ganglia more specific and nearer to target organ
- 1:3 pre-vs postganglionic nerves: localised, specific actions directed at one organ
- Neurotransmission
  - acetylcholine preganglionic
  - acetylcholine postganglionic: smooth muscle cells and cardiac muscle and pacemaker: inhibitory influence.
- Less active during stress
- Supporting energy conservation, reproduction, digestion
Autonomic control of heart rate

- good example for graded, reciprocal regulation by sympathetic and parasympathetic division of ANS
- sympathetic: norepinephrine in SA-node (via sympathetic chain) → heart rate increases
- parasympathetic: acetylcholine in SA-node (via vagus nerve) → heart rate decreases
- (para)sympathetic outflows to SA-node

- parasympathetic (via vagus nerve): heart rate decrease
- sympathetic (via sympathetic chain): heart rate increase

**Electrocardiogram (ECG/EKG)**

- registration of electric activity of the heart
- Willem Einthoven: Nobelpreise Medicine
The EKG breaks down each heartbeat into a series of electrical waves. Three of the waves, the P wave, the QRS complex and the T wave, are associated with the heart's contractions. The P wave reflects activity in the heart's upper chambers. The QRS complex and T wave reflect activity in the lower chambers.
- Heart rate (HR) - expressed in ‘beats per minute’ (bpm)
  - count number of R peaks per minute

- Heart period (HP) - interbeat interval (IBI) in msec
- time between R peaks (R-R interval)

- Heart rate change to simultaneous vagal and sympathetic stimulation

**HR change to simultaneous vagal and sympathetic stimulation**

![Graph showing heart rate change](image1.png)

**Legend**:
- S=4
- S=2
- S=0
- V=0
- V=4
- V=8


V=8: vagal and sympathetic stimulation → no increase in HR
Heart rate variability

IBI Series (real time)

.12-.40 Hz filtered IBI Time Series
Individual differences in heart rate variability

- heart rate variability = informative
- vagal influences ↗ then heart rate variability ↗
- vagal influences on SA-node occur at respiratory rhythm
  - respiratory ‘gating’ of autonomic outflow
  - only vagal influences allow for such rapid fluctuations in heart rate
- respiratory sinus arrhythmia (RSA)
  - naturally occurring variations in heart rate at respiratory rhythm
  - measure of parasympathetic nervous system activity
  - inspiration: less vagal outflow, heart accelerates
  - expiration: more vagal outflow, heart decelerates

![Electrocardiogram](image)

- magnitude of heart rate oscillations (trillingen) at the respiratory rhythm (RSA) =
  - index of vagal (parasympathetic) activity
- general significance of HRV: indicates the individual flexibility of the heart activity to fit endogenous and exogenous demands
- RSA correlates with
  - stress, depression, anxiety
  - cardiac mortality
  - emotional regulation
  - executive functioning
- groups matched on age, sex, BMI, alcohol use
- similar level of depression among MDD groups
- no medicated patients, no individuals with comorbid physical illness
- 2 min resting state ECG measurement
- results: --> reduced HRV in MDD (time and frequency domain)
  --> reduced HRV most pronounced in MDD and GAD

MDD = major depression

GAD = general anxiety disorder
The role of vagal function in the risk for cardiovascular disease and mortality

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Abstract

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide. The understanding of the risk factors for CVD may yield important insights into the prevention, etiology, course, and treatment of this major public health concern. We review the evidence for the role of vagal function in the risk for cardiovascular disease and mortality. Using a broad range of indicators of vagal function including resting heart rate, heart rate recovery, heart rate variability, and baroreflex sensitivity we show that decreased vagal function is associated with an increased risk for morbidity and mortality. These effects are independent of traditional risk factors. Moreover, we show that decreased vagal function is associated with both traditional and emerging risk factors as well as modifiable and non-modifiable risk factors. Most importantly, we provide evidence to support the notion that decreased vagal function precedes the development of a number of risk factors and that modification of risk profiles in the direction of lower risk is associated with increased vagal function. We close with a brief overview of the neural correlates of vagal function and suggest that a model of neurovisceral integration may provide a unifying framework within which to investigate the impact of risk factors, including psychosocial factors, on cardiovascular disease.

Keywords: Cardiac vagal control; Cardiac vagal tone; Heart rate variability; Risk factors; Heart disease; Hypertension

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A hierarchy of homeostatic controls: endocrine stress responses

- Endocrine stress responses: 2 parallel responses
  - adreno-medullary response (left)
  - adreno-cortical response (right)
Figure 4.6  Neuroendocrine components of the stress response. Functional organization of the systems controlling release of the primary stress hormones cortisol, beta-endorphin, and epinephrine.

CRF: corticoreleasing factor
ACTH: adrenocorticotropic hormone
Adreno-medullary response

- hypothalamus (paraventricular nucleus)
  ↓
- brain stem (nucleus of the solitary tract)
  ↓
- adrenal medulla
  ↓
- Release of catecholamines into blood
  ↙ epinephrine
  ↘ norepinephrine
- B-adrenoreceptors on viscera (enhancing sympathetic activity)
- α-adrenoreceptors on viscera (negligible effect)

Adreno-medullary response is controlled by SNS. Adrenal medulla is activated by sympathetic preganglionic fibers that originate in the brain stem.

- Adreno cortical response
  - see later
  - ‘normal’ vs ‘stress’ levels of cortisol

Normal cortisol levels

- Permissive: enables autonomic and physiological regulation
- Cortisol is released by adrenal cortex
- Circadian pattern
- 3 negative feedback circuits for ‘normal’ cortisol levels
  - hypothalamus: via cerebrospinal fluid in 3rd ventricle
  - pituitary: cortisol reaches pituitary directly through the blood
  - hippocampus:
    - low cortisol levels: hippocampus signals this to hypothalamus --> stimulates CRF release
    - high cortisol levels: inhibition of signals from hippocampus to hypothalamus --> less CRF release
“Stress” levels of cortisol

- Potentiates sympathetically mediated release of glucose and fat (supports fight/flight)
- Regulatory action: preventing the stress response to damage the organism. Cortisol ensures we have some energy left after the fight/flight response. Without cortisol stress would have a damaging effects. Thus cortisol prevents a threat to homeostasis.

**B-endorphine**

- Produced by pituitary
- Agonist of opiate receptors in CNS
- Analgesia
  - in anticipation of potential injury or pain
  - regulating mood during negative events
- When hypothalamus secretes CRF --> pituitary releases same amount of B-endorphine and ACTH.
A hierarchy of homeostatic controls: hypothalamus

- Organizes behavior important for survival
- Grouping of autonomic, endocrine and skeletal-motor nuclei
  - inputs to brain stem affecting autonomic regulation
  - control of endocrine functions: release of CRF (corticotropin releasing factor)
  - AVP (antidiuretic hormone)
  - posture and locomotion
- Connections with higher brain centers (limbic system and frontal cortex)
  - limbic system (emotion)
  - frontal cortex (cognition)
- Coordinated stress responses are possible without higher brain centers!
- Experiment: Cannon & Bard: Cat preparation
(a) The cat's cerebral cortex has been removed above the level of the hypothalamus. The cat was able to produce a fully “sham-rage” display to stimuli such as stroking. This sham rage was stereotyped and not focused on a specific target. This preparation demonstrated that the hypothalamus and lower structures had the necessary motor and visceral integrative networks to produce this fully integrated response.

(b) The cat's hypothalamus has been cut between its anterior and posterior divisions. Most of the elements of the sham rage were retained, indicating that the posterior hypothalamus retained the essential structures to coördinate behavioral and visceral outputs.

(c) The cut has been made below the hypothalamus. The response of the cat to tactile stimuli became fragmented and poorly coördinated, indicating that the visceral and motor components of expression of the emotions were no longer jointly regulated by the hypothalamus.
Class 2: central integration of the stress response = higher brain centers

Appraisal model of psychological stress

- Primary appraisal = threat?
  - = automatic
- Secondary appraisal = how to deal with threat?
- Cognitive vision: Appraisals determine nature and strength of our psychological reactions and their physiological consequences.
  - Assumption: people evaluate their environment constantly in a very conscious way.
They choose coping mechanisms in a voluntary matter. Critics: appraisals can also occur in an involuntary matter.

- Psychological stress = individual subjective perception of threat
- Psychological stressors:
  - achieve threat value not from their physical ability to do harm but from their appraised threat value
  - are not equally stressful to all persons
  - persons vary in their ability to cope with them
  - physiological systems that respond to them = systems that respond to physical threats to homeostasis
- Coping responses:
  - problem-focused: change problem/event itself, gain information, increase coping options --> can reduce threat
  - emotion-focused: psychological changes to reduce emotional disruption due to event, minimal effort to alter event itself
- Best response depends from situation:
  - problem-focused: lots of time/energy
  - emotion focused: less energy on that moment, but on long term basis more energy because of constantly drain of resources.
- After coping: re-evaluate threat --> coping responses are constantly being modified.
- Goal of coping: reducing activation of CNS.

- Original cognitive version:
  - continuous conscious evaluation of events and coping possibilities
  - conscious ‘beliefs and commitments’ determine threat value
- More complete version:
  - appraisals can occur also outside/with decreased awareness, but yet cause similar responses.
  - primary appraisals due to conditioned prior experiences
  - secondary appraisals due to behaviorally conditioned coping strategies from prior experiences.
- Highly cognitive appraisals and automatic conditioned appraisals possible
Brain structures underlying appraisals

- Above hypothalamus:
  - perception and interpretation of external events
  - initiation of responses to these events, behavioral plans
  - top-down control over homeostasis

- External event → stress response: 5 components
  1) sensory intake and interpretation of environment
  2) emotions based on appraisal
  3) initiation of autonomic and endocrine responses
  4) feedback to cortex and limbic system
  1 + 2 + 3 + 4 = how higher brain centers influence the ‘homeostatic apparatus’
  (hypothalamus-brainstem-ANS)
  5) autonomic and endocrine outflow

DLPFC = dorsolateral prefrontal cortex

- Working memory functions: directing attention, conscious evaluation of events, action planning, decision making
- ‘cognitive’
VMPC = ventromedial prefrontal cortex

- Visceral/limbic inputs
- Interface between emotion and cognition
- Emotion regulation
- Input of affect in decision making (ethical dilemma tasks for example)

- Phineas Gage: his VMPC was damaged. He could make rational decisions but there were no emotions involved.

Limbic system

Figure AB-16: Limbic System

Diagram colors are consistent with Figure AB-17.
Limbic system
- complex set of brain structures that lies on both sides of the thalamus, right under the cerebrum.
- It includes the olfactory bulbs, hippocampus, amygdala, anterior thalamic nuclei, fornix, column of fornix, mamillary body, septum pellucidum, habenular commissure, cingulate gyrus, parahippocampal gyrus, limbic cortex, and limbic midbrain areas.

Crucial in generating emotions that motivate an organism to avoid threats and approach things important for survival

Memory of experiences with motivation relevance

Amygdala: central role

Cingulate gyrus:
- communication with sensory and motor areas of the cortex
- has control over hypothalamus and brainstem when a response to external events is required
- in case of (perceived) danger: integration of fight/flight state --> acute stress reaction

Amygdala

- Sensory inputs from thalamus, hippocampus and cortical areas
- Outputs to prefrontal cortex and hypothalamus
- Ability to look forward to potential threats
  - innate (aangeboren)
  - learned (Pavlovian fear conditioning)
Quick and dirt route vs slow and precise route

- Quick and dirt route: info from thalamus directly to amygdala. Short and fast but less precise information. Ability to react even before we know exactly what’s going on = advantage in dangerous situations.
- Slow and precise route: info from thalamus to cortex to amygdala. More accurate assessment of situation.
- Example: on a walk, you see a long, narrow shape at your feet. This snake-like shape sets in motion the physiological reactions of fear. This happens very quickly, via the short route. But this same visual stimulus, after passing through the thalamus, will also be relayed to your cortex. A few fractions of a second later, the cortex, thanks to its discriminatory faculty, will realize that the shape in fact is just a garden hose. Your heart will stop racing and you’ll just have had a moment’s scare. But if your cortex had confirmed that the shape really was a snake, you probably had run with all the alacrity that the physiological changes triggered by your amygdala allowed. Thus, the fast route from the thalamus to the amygdala does not take any chances. It alerts you to anything that seems to represent danger. The cortex then makes appropriate adjustments. The hippocampus can give information about the context.
Amygdala activation in response to negative vs neutral pictures

- Negative pictures elicited more activation in the amygdala than neutral pictures

MR signal change in the amygdala to negative vs neutral pictures related to trait negative affect

![Scatter plot of the relation between MR signal change in the right amygdala in response to unpleasant versus neutral pictures assessed with functional MRI and dispositional negative affect. Amygdala activation is higher in persons with NA, for both sets of stimuli (neutral and negative).](image-url)
Major projections from amygdala

- Stria terminalis (terminating at bed nuclei of the stria terminalis, BNST): connects amygdala with hippocampus
- Ventral amygdalofugal pathway: connects amygdala with nucleus accumbens (appetitive behavior)
Hippocampus

- Declarative (explicit) memory
- Processing sets of stimuli and contextual information
- Strong connections with amygdala

Anterior cingulate cortex (ACC)

- Conflict monitoring, executive functions
- Choosing among behavioral alternatives under motivational conditions
- Visceral integration/antinociception (reducing sensitivity to painful stimuli)
- Emotion processing
Basal ganglia

- Group of brain structures around thalamus involved in the control of movement, reward, motivated behavior
- Together, they constitute a system facilitating/inhibiting movement
- Stria terminalis = nucleus caudatus and putamen

5 components of psychological stress: 1 sensory intake

**Thalamus**: central way station for incoming sensory information

↓

**unimodal cortical sensory association areas**: raw sensory information is increasingly elaborated with stored information related to that sensory modality --> familiar quality of objects

↓

**polymodal association areas**: integration of information from different unimodal areas

example: inferior temporal gyrus combines auditory and visual information

↓

input to limbic structures (affect)

↓

input to prefrontal cortex (cognitive meaning)
Integration of visual and auditory input

2 Generating emotions based on appraisal processes

- prefrontal-limbic connections
  - VMPC & ACC: visceral coloration of thoughts
  - Projections from amygdala and hippocampus to PFC and to basal ganglia
  - Link between thoughts/events and emotions
  - Goal: give meaning and emotional value to input
  - Connections --> emotional responses
    --> psychological stress responses
<table>
<thead>
<tr>
<th><strong>Hippocampus</strong></th>
<th><strong>Amygdala</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Declarative memories (facts, events)</td>
<td>Emotional states/memories (motivation)</td>
</tr>
<tr>
<td>Damage/removal impairs ability to form new memories of daily experiences</td>
<td>Forms Pavlovian conditioned associations between external world and intern feelings about it</td>
</tr>
<tr>
<td>Example: patient HM: even after years of living in a new neighborhood unable to develop map of new neighborhood, needed help during walks</td>
<td>Damage impairs ability to form these associations</td>
</tr>
<tr>
<td>Example: -Pavlov’s dog: external event (bel) linked to internal state (taste) - amygdalecctomized animals</td>
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➤ Together, essential for normal set of experiences of events and their emotional/motivational meanings
2 pathways from hippocampus and amygdala to anterior cingulate cortex:
- highly interconnected areas
- integration of sensory input with experience and emotional/motivational significance

Right: amygdala --> anterior cingulate gyrus
Left: hippocampus --> dorsolateral prefrontal cortex
Both pathways integrate cognition and emotion
Prefrontal-limbic connections: critical for primary and secondary appraisals as outlined by Lazarus and Folkman model of psychological stressors.

3 Initiation of behavioral, autonomic and endocrine responses

- Hypothalamus:
  - Inputs from
    - amygdala (via bed nucleus of stria terminalis; direct)
    - orbito-prefrontal cortex (via medial forebrain bundle)
  - Outputs to
    - brainstem pons and medulla
      - Skeletal motor programs
      - Endocrine activations
      - Autonomic activations

= expressions of emotions/stress responses

4 Feedback to cortex and limbic system: central feedback subsystem

- Network of brainstem nuclei that provides the CNS with feedback of its own activities
  - determines global behavioral state (be active vs go to bed)
  - Treshold to short- and longterm experience of pos/neg affect
- Pontine reticular formation
  - diffuse collection of fibers and nuclei
  - connections between sensory systems and systems allowing for behavioral and physiological responses
- Important are its aminergic nuclei (locus ceruleus, raphe nuclei, ventral tegmental area)
  - synthesize monoaminineurotransmitters
    - raphe nuclei --> serotonin
    - locus ceruleus --> norepinephrine
    - ventral tegmental area --> dopamine
  - Input from frontal-limbic areas and amygdala (via BNST)
  - outputs to all other CNS structures (especially to frontal-limbic, hypothalamus)
general coordination of arousal levels and affective tone, dependent on amygdala activation and frontal-limbic processes

Norepinephrine

The **locus coeruleus** contains most of the neurons that produce **norepinephrine** in the brain. They send projections to just about every part of the central nervous system. Located in the dorsal portion of the pons, these cells are strongly activated by new sensory stimuli. They play a role in regulating vigilance and attentiveness and are inactive during sleep. Overactivity of this system can cause anxiety, while underactivity can lead to depression.
Serotonin

The neurons of the Raphe nuclei release serotonin as a neurotransmitter. These neurons are grouped into about 9 pairs, distributed along the entire length of the brainstem. They project very widely throughout the central nervous system. The more rostral nuclei innervate the cortex and the thalamus, while the more caudal nuclei innervate the cerebellum and the spinal cord. These latter nuclei appear to work in conjunction with the noradrenergic neurons; they are active during waking periods and quiet during sleep. In addition to being involved in the sleep/wake cycle, they also appear to affect mood.

Mood disorders

Dopamine

The two groups of neurons that diffuse dopamine are located in the lower portion of the midbrain. The substantia nigra (black substance) projects to the striatal structures (caudate nuclei and putamen). The degeneration of this nigrostriatal pathway that accompanies Parkinson's disease produces the trembling and the difficulty in initiating movement that characterize this illness. Other dopamine-producing cells project from the ventral tegmental area to the frontal cortex and to most of the structures in the limbic system. This system appears to be involved in reinforcing certain behaviours by associating them with pleasurable sensations. It also seems to be associated with the mechanisms involved in substance dependencies and in schizophrenia.
Dopamine release during euphoria by nucleus accumbens.
Reward.
Pleasurable experiences --> long term mood

Feedback to cortex and limbic system: central feedback subsystem

**Figure 6.9** The central feedback subsystem. The outputs from the central nucleus of the amygdala (CEN) to the bed nucleus of the stria terminalis (BNST) and nucleus accumbens (Accumb.) and descending pathways to and through the hypothalamus to the brainstem aminergic nuclei. The ascending projections are directed to all parts of the cerebral hemispheres, with especially heavy representation to hypothalamus and frontal-limbic areas.
5 Autonomic and endocrine outflow

Startle reflex and emotions

- Response matching hypothesis:
  - startle reflex is a defensive response
  - startle magnitude increased when anxious (fear potentiated startle FPS)
  - startle magnitude decreased during pleasant emotions
Measurement of the startle reflex

- Elicited with brief burst of white noise (startle probe) presented over headphones
- Eyeblink response is indexed by recording electrical activity in the orbicularis oculi muscle with electromyography (EMG)

Neural circuitry of startle reflex

Fear conditioning/ → amygdala
shock sensitization ↓
  nucleus reticularis pontis caudalis (RPC)
  cochlear root spinal and facial neurons motorneurons
  abrupt noise (probe) startle reflex

- Lesions of the amygdala block “fear potentiated startle reflex” (FPS)
- Electrical stimulation enhances startle reflex
Affective picture viewing paradigm

- 36 pictures (12 pleasant, 12 neutral, 12 unpleasant)
- 6s presentation of each picture
- 9 unpredictable probe presentations within each valence
- Results: startle magnitude: pleasant < neutral < unpleasant
- Addition: visual or acoustic probes:
  - startle response to acoustic probe during picture viewing vs startle response to visual probe during picture viewing was compared
  - regardless of probe modality, same direction of linear valence effect was observed

Cortical inhibition of stress responses by reappraisal

- Reappraisal:
  - changing the emotional response to a situation by changing the meaning of the situation
  -- which emotion (quality)
  -- intensity of emotional experience (quantitative)
- Types:
  - reinterpreting
  - distancing

“Maintain”: attend to, be aware of, experience naturally (without trying to alter) the emotional state
“Surpress”: reinterpret the content of the picture so that it no longer elicits a negative
response
- strategies:
  --> transforming the scenario into positive terms (e.g. women crying outside of a church
could be alternatively interpreted as expressing tears of joy from wedding ceremony rather
than of sorrow from a funeral).
  --> rationalizing or objectifying the content of the pictures (e.g. a woman with facial bruises
could be translated as an actor wearing makeup rather than a victim of domestic abuse).

![Graph showing intensity of negative affect over blocks]

**Figure 2.** Subjective ratings of intensity of negative affect following each Maintain and Suppress block across the experiment. Significant effect of condition but not of time or condition-by-time interaction.

Self reported emotion.

- Brain activation:
  - negative pictures: amygdala, insula, mPFC
  - suppression: activation in dorsal ACC, DLPFC, DMPFC, VLPFC, OFC
Exam questions:

1) Discuss the mono-aminergic nuclei
2) Explain fear potentiated startle
3) Locate the VMPC on the figures below and discuss its function
4) Explain: “the amygdala allows an organism to recognise a potential danger.”
5) Discuss: the amygdala plays an important role in the generation of bodily responses to stress.
Class 3: Endocrine stress responses

INTRODUCTION

The sympathetic adrenal medullary pathway (SAM) = first part of the stress response

- Release of adrenaline and noradrenaline. This activates the body for sudden action, such as fight/flight.
The hypothalamic-pituitary-adrenocortical axis (HPA): second part of stress response

- Release of glucocorticoids such as cortisol. This helps the body cope with stress.
Adrenalin and cortisol are closely linked and form an integrated stress response:
- Adrenals release both hormones
- Central CRF output initiates both axes
- Adrenalin increases secretion of ACTH (pituitary)
- Cortisol regulates release of adrenalin (via feedback of cortisol at the PVN hypothalamus)

**Figure 4.6** Neuroendocrine components of the stress response. Functional organization of the systems controlling release of the primary stress hormones cortisol, beta-endorphine, and epinephrine.
Example: Trier social stress task

- Panel of interviewers
  - neutral (stoic, non encouraging)
  - “trained to look at intelligence verbal and nonverbal”
- 5 minute preparation
- 5 minute interview
  - “please continue”: if the participant stops talking before 5 minutes are filled, they instruct him to go on.
- 5 minute math task (serial substraction)
- Induces stress
- first 5 minutes: anticipatory stress phase = preparation
  - next 5 minutes: presentation
  - last 5 minutes: math test
- TSST increases levels of substances known to indicate activation of the HPA-axis (core driver of physiological stress). These include ACTH, cortisol,... Also the heart rate increases.
Stress hormones

- Cortisol and adrenaline (epinephrine)
  - **Feed forward** (in anticipation of stress): higher brain structures influence the release of cortisol and adrenalin into the blood
    - allowing for the coordination of stress responses across different organ systems and the optimization of the stress response without losing homeostasis.
  
  - **Feedback** (during stress)
    - of acute hormonal reactions
    - altered gene-expressions in frontal-limbic structures modulating stress
responsivity in the longer term
--> modulation of emotional memory and therefore also of future stress appraisals

Example: Trier social test task

- Why is this stressful?
  - primary appraisal:
    social evaluative threat
    perception of bodily symptoms
  - secondary appraisal:
    uncontrollable: limited time to prepare and lack of information/feedback
    lack of resources or coping mechanisms

Comparing TSST and control task

- Job interview vs talk about movie/book/vacation
- Observers/judges vs no judges
- Difficult vs easy math problem

![Graph](attachment:image.png)

*Figure 1* Salivary cortisol concentrations (mean and S.E.M.) of participants exposed to the TSST or the placebo TSST. As expected, participants under the TSST condition showed elevated cortisol concentrations 10 min after the TSST. Participants, who were treated with the placebo version of the TSST showed a decline during the course of the experiment.
Salivary cortisol levels are higher in the TSST task than in the control task.

Salivary alpha-amylase levels are higher in the TSST task than in the control task.

Appraisal of arousal and bodily symptoms

Reappraising arousal improves cardiovascular and cognitive responses to stress.

CRF SYSTEM

Corticotropic releasing factor

Functions: triggering HPA-sequens

= neurotransmittor: in various brain structures involved in ‘appraisals’ and autonomic control (cortex, limbic system, nuclei brain stem)

CRF releasing cells:
- PVN hypothalamus
- amygdala
- prefrontal cortex, insula, cingulate gyrus
The CRF system

The core of the HPA-system is shown in the lower right part of the system. The hypothalamus contains two populations of neurons that synthesize CRF: CRF only and CRF-AVP. CRF-AVP cells exert greater effect on the pituitary than CRF alone. The negative feedback of cortisol is 10 times more effective on CRF-only cells than on CRF-AVP cells. The CRF-AVP cells project to the brainstem to activate fight-flight related activities of the autonomic nervous system and stress-related posture and locomotion. A second set of CRF neurons is shown in the central nucleus of the amygdala and the bed nuclei of the stria terminalis (BNST). Projections from the BNST act on the brainstem and lateral hypothalamus and paraventricular nucleus. The cortex, amygdala, and BNST all have significant numbers of CRF cells. Cortisol acts on all cell types in the periphery and the CNS. The figure indicates that epinephrine and cortisol act on immune system cells. One effect of these actions is that cytokines are released. These act indirectly to influence the CNS, notably to increase CRF-AVP secretion by the hypothalamus.

The Corticotropin Releasing Factor System

Figure 7.1 The corticotropin releasing factor (CRF) system. The core of the hypothalamic-pituitary-adrenocortical system is shown in the lower right part of the figure. The paraventricular nucleus is shown containing two populations of neurons that synthesize CRF: CRF only and CRF-AVP (arginine vasopressin). CRF-AVP cells exert greater effect on the pituitary than CRF alone (deBold, 1984). The negative feedback of cortisol is 10 times more effective on CRF-only cells than on CRF-AVP cells. The CRF-AVP cells project to the brainstem to activate fight-flight-related activities of the autonomic nervous system and stress-related posture and locomotion. A second set of CRF neurons is shown in the central nucleus of the amygdala and the bed nuclei of the stria terminalis (BNST). Projections from the BNST act on the brainstem and lateral hypothalamus and paraventricular nucleus. The cortex, amygdala, and BNST all have significant numbers of CRF cells. Cortisol acts on all cell types in the periphery and the CNS. The figure indicates that epinephrine and cortisol act on immune system cells. One effect of these actions is that cytokines are released. These act indirectly to influence the CNS, notably to increase CRF-AVP secretion by the hypothalamus.
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The figure indicates that epinephrine and cortisol act on immune system cells. One effect of these actions is that cytokines are released. These act indirectly to influence the CNS, notably to increase CRF-AVP secretion by the hypothalamus.

CRF cells from central nucleus of the amygdala:
Primary output to
- hypothalamus
- brain stem
- frontal-limbic areas
--> these three project to aminergic nuclei of brainstem
The actions of CRF at different levels of the stress response. (1) CRF nerve terminal in the median eminence release CRF into the hypothalamo-hypophyseal portal system and stimulate ACTH release from the anterior pituitary. (2) CRF directly stimulates cortisol and catecholamine synthesis from the adrenal gland. (3) CRF stimulates noradrenergic neurons in the locus coeruleus. (4) CRF mediates a series of behaviors through actions on cortical and limbic brain regions. (5) CRF transcription is negatively regulated by glucocorticoids in the hypothalamus, but positive regulation has been reported in limbic brain regions.

CRF system schematic:

- Hypothalamus (synthesis CRF) → adrenal gland (secretes cortisol)
- Hypothalamus (synthesis CRF) → pituitary (secretes ACTH)
- CRF cells in amygdala → Brain stem (fight/flight)
- Frontal-imbic areas (behavior) → brain stem
<table>
<thead>
<tr>
<th>Brainstem CRF Target</th>
<th>Functions of Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Locus ceruleus</strong></td>
<td>Source of most noradrenergic cells projecting to the rest of the central nervous system. Activation and coordination of CNS functions. May act to stimulate the extrahypothalamic central CRF system. Antinociception.</td>
</tr>
<tr>
<td><strong>Nucleus paragigantocellularis</strong></td>
<td>Programmed outputs associated with emotion-related postures and locomotion.</td>
</tr>
<tr>
<td><strong>Periaqueductal gray area</strong></td>
<td>Integrates behaviors with autonomic responses during significant events, especially during fight-or-flight. Enhanced startle during amygdala activation. Antinociception.</td>
</tr>
<tr>
<td><strong>Nucleus of the solitary tract</strong></td>
<td>The major autonomic integrating center in the brainstem. Receives inputs from all of the visceral sensory nerves, especially the vagus. This information is distributed to autonomic nuclei and higher centers, including hypothalamus and amygdala. Sends inputs to periaqueductal gray area</td>
</tr>
<tr>
<td><strong>Intermediolateral cell column</strong></td>
<td>Descending outputs to the sympathetic nervous system.</td>
</tr>
</tbody>
</table>
Central receptors for cortisol

- 2 types of receptors:
  - Type I (MR, mineralocorticoid)
    --> sensitive to low levels of cortisol
    --> negative feedback regulation in function of normal, metabolic, circadian variations
  - Type II (GR, glucocorticoid)
    --> 10-20 < sensitive to cortisol
    --> ‘stress’ levels of cortisol
    --> highly prevalent in amygdala
    --> modulate gene expression of cell they occupy

<table>
<thead>
<tr>
<th>Region</th>
<th>Type I</th>
<th>Type II</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>414</td>
<td>305</td>
<td>719</td>
<td>45</td>
</tr>
<tr>
<td>Lateral septum</td>
<td>51</td>
<td>194</td>
<td>245</td>
<td>15</td>
</tr>
<tr>
<td>Nucl. of solitary tract</td>
<td>76</td>
<td>123</td>
<td>199</td>
<td>13</td>
</tr>
<tr>
<td>Central amygdala</td>
<td>9</td>
<td>112</td>
<td>121</td>
<td>8</td>
</tr>
<tr>
<td>Locus ceruleus</td>
<td>41</td>
<td>75</td>
<td>116</td>
<td>7</td>
</tr>
<tr>
<td>Paraventricular nucl.</td>
<td>28</td>
<td>59</td>
<td>87</td>
<td>6</td>
</tr>
<tr>
<td>Supraoptic nucl.</td>
<td>0</td>
<td>60</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>Raphe nucl.</td>
<td>0</td>
<td>44</td>
<td>44</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Regions were punched out from frozen sections of brains of rats perfused at sacrifice with saline. Data represent B_max (fmole/mg protein) from Scatchard analyses. KD to CORT Type 1: 0.5–1 nM; Type 2: 3–5 nM.
Central effects of ‘stress’ levels of cortisol

- Modulation of
  - sensory thresholds
  - learning and memory
  - mood (general anxiety)
- CRF producing neurons and receptors for cortisol in
  - ventrolateral and orbitofrontal PFC
  - ACC
  - insular cortex
- hippocampus
- amygdala
---> appraisal of events and emotions

➢ Thus, actions of cortisol are more complex than just the negative feedback regulation. Cortisol can make the organism function even in high stress/arousal states.

Amygdala sensitization by cortisol

➢ Experiment:
- Corticosterone implant at CEN amygdala in exp group; sham surgery in control group
- Acute corticosterone response present in both groups
- Corticosterone production in response to stress decreased rapidly in control group, whereas it continued in the experimental group - < explorative behavior in exp group
- greater gene expression for CRF in CEN
  ➢ Exposure of CEN amygdala to cortisol --> sensitization
  ➢ Increased and prolonged production of CRF
  - feedback regulation of cortisol less effective
  - increased and continued anxiety responses

Amygdala sensitization by cortisol: implications for health?

➢ Irritable bowel syndrome
  - gastro-intestinal pain without known organic cause
  - psychiatric co-morbidity
  - women > men
  - stress related
  - Exp: corticosterone implant in rat. --> greater pain sensitivity to balloon distention in gut+anxious behavior
Posttraumatic stress disorder (PTSD)
- < volume hippocampus = vulnerability factor for PTSD
- inability to adequately regulate cortisol during trauma
- greater exposure of amygdala to cortisol
- large amounts of cortisol inhibit growth of new hippocampal cells and speed up destruction of existing cells

↓
Sensitization of central CRF-system because of great exposure of cortisol to amygdala? --> permanent shift to a more reactive HPA-axis.

Modulation of long term memory

- Cortisol and adrenalin facilitate consolidation of emotional events (declarative), and therefore, influence future appraisals.
- Experiment:
  - experimental group: hydrocortisone
  - control group: placebo
  - better memory for emotional (pos/neg) pictures in experimental group 1 week later; no group difference for neutral pictures

Modulation working memory

- Greater cortisol responses to stress task associated with worse performance on a working memory task

SUMMARY

Stress endocrine secretion and regulation of long-term stress reactivity

- Stress endocrine secretion and regulation of long-term stress reactivity:
  - how can stress endocrine feedback alter adaptive behavior?
  1) altered gene expression in the CRF system
  2) stress reactions influence formation of long-term, declarative memory
  3) amygdala sensitization + loss of hippocampal volume --> alter cognitive processes --> health in general
Hierarchy of autonomic and endocrine controls over homeostasis

- Functional autonomy of individual organs
- Autonomic and endocrine controls
- Brainstem
- Hypothalamus
- Higher brain centers (cortex + limbic system) --> behavior
Figure 4.1 Schematic of controls over organic function. The diagram indicates that individual organs have self-regulating capacity. This self-regulation is determined by internal reflexes and the actions of autonomic ganglia located in or near them. Local regulation is modulated in turn by descending influences from the autonomic nervous system, the brainstem, the hypothalamus, and higher centers in the central nervous system.

- Hierarchy of controls --> maintain homeostasis
Threat → stress → coping behaviors → reducing activity of SNS → reduce agitation associated with limbic activity = reward

The formation of psychological stress responses revisited

- Primary + secondary appraisal → physical events that influence state of body
- Frontal lobes (working memory) interact with limbic system and respond in relation to prior experiences
- Negative emotional responses: interaction between prefrontal cortex, amygdala, hippocampus, frontal-limbic areas (anterior cingulate gyrus, ventromedial prefrontal cortex, nucleus accumbens)
- Amygdala → outputs to hypothalamus → development of adaptive neuroendocrine and autonomic responses
- CRF system: binds together functions of cortex, brainstem, and hypothalamus → integrated outflow
- Regulatory systems: under control of physical AND psychological stressors
- Primary + secondary appraisal = basis for emotional states → physiological responses
- Appraisal processes = highest level of control over our homeostatic functions
- How do ideas have power over our body?
  - appraisals → emotional state → physiological response

CHRONIS STRESS AND HPA ACTIVATION

Chronic stress, cortisol and health

- Regulatory functions of cortisol:
  - CNS: emotion, learning, memory
  - Metabolic: glucose regulation
  - Immunity: duration and magnitude of inflammatory response + maturation lymphocytes
- Chronic stress?
  - hypercortisolism:
    - atherosclerosis
    - insuline resistance
    - adiposity (=obesity)
    - excessive anxiety
    - depression
    - decreased immune function
PTSD
- hypocortisolism:
chronic fatigue syndrome
irritable bowel syndrome
auto-immune diseases (RA, allergy, PTSD)

Predictors of hypo/hyper-activity of the HPA-axis

1) Time
2) Nature or stressor
3) Key emotion triggered by stressor
4) Controllability of stressor
5) Psychiatric characteristics

Time since onset

➢ Increase of cortisol at beginning of stressor, but decreases during time
   explanation: negative feedback of HPA-axis. Raised levels of cortisol decrease
   secretion of CRH and ACTH.

Nature stressor

➢ Psychological vs physical threat?
   Different forms of stress --> different hormonal responses?
➢ Traumatic vs not traumatic?

Key emotion

➢ Shame? Loss?

Controllability stressor

➢ > acute stress
➢ < chronic stress
Psychiatric characteristics

Psychiatric syndrome $\rightarrow$ HPA-axis goes up or down

Chronic stress
$\downarrow$ no diagnosis $\rightarrow$ ‘normal’ HPA axis

Indexing HPA-activity

- Circadian pattern
- Cortisol output (saliva, urine, blood)
- CRH in cerebrospinal fluid
- ACTH in blood
- Sensitivity negative feedback circuit
  - dexamethasone
  - CRH (pituitary)
  - ACTH (adrenal cortex)
- Sensitivity of tissue to cortisol
  - cortisol binds to receptor, translocation to nucleus, genexpression
  - more receptors = more sensitive to cortisol
  - # GR (down/upregulation): indication of recent exposure to cortisol

Meta analysis

- Medical and psychological databases 1950-2000
- Specifying each term
- Inclusion criteria: chronic stress, measure of HPA activity, effect size (ES) calculation possible, control group
- 1) effect size for each study
  2) aggregated ES across studies that investigate similar predictor-outcome variables
  3) test whether aggregated ES not equals 0
- The notion that stress contributes to disease by activating the HPA-axis is featured prominently in many theories. The research linking stress and the HPA axis is contradictory, however, with some studies reporting increased activation and others reporting the opposite. Our meta-analysis of this area showed that some of the variability in the HPA-response is attributable to stressor and person features. Timing is an especially critical element, as hormonal activity is elevated at stress onset but
reduced as time passes. Stress that threatens physical integrity, is traumatic in nature, and is largely uncontrollable, elicits a high, flat diurnal profile of cortisol secretion. Finally, HPA activation is shaped by the person’s response to stress; cortisol output increases with the extent of subjective distress and is generally reduced in those who develop PTSD. These findings highlight the importance of incorporating stressor and person features into models of chronic stress and HPA activity. They also suggest that relations among stress, cortisol and diseases are likely to be more complex than previously acknowledged. Because chronic stress can elicit such a wide variety of HPA responses, its impact on disease outcomes will be varied and depend on whether high vs low cortisol is pathogenic. The next wave of models will need to be refined to acknowledge this complexity. With better theories and further research of the nature suggested by the meta-analysis, the pathways through which chronic stress ‘gets under the skin’ to influence disease will come into clearer focus.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Studies of combat/war</th>
<th>Studies of abuse/assault</th>
<th>Studies of death/loss</th>
<th>Studies of caregiving</th>
<th>Studies of disaster</th>
<th>Studies of job loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since onset (Mdn, range)</td>
<td>300.0 (1–720)</td>
<td>69.5 (1–400)</td>
<td>61.4 (1–360)</td>
<td>42.0 (6–144)</td>
<td>12.0 (1–78)</td>
<td>18.0 (8–24)</td>
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<tr>
<td>Physical threat rated as likely (%)</td>
<td>100.0</td>
<td>100.0</td>
<td>8.3</td>
<td>0.0</td>
<td>62.5</td>
<td>0.0</td>
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<tr>
<td>Social threat rated as likely (%)</td>
<td>30.0</td>
<td>50.0</td>
<td>91.7</td>
<td>100.0</td>
<td>12.5</td>
<td>100.0</td>
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<tr>
<td>Trauma rated as likely (%)</td>
<td>100.0</td>
<td>100.0</td>
<td>36.4</td>
<td>0.0</td>
<td>100.0</td>
<td>0.0</td>
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<tr>
<td>Rated as likely to be uncontrollable (%)</td>
<td>100.0</td>
<td>100.0</td>
<td>91.7</td>
<td>22.2</td>
<td>87.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Feelings of loss rated as likely (%)</td>
<td>100.0</td>
<td>44.0</td>
<td>100.0</td>
<td>100.0</td>
<td>75.0</td>
<td>100.0</td>
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<tr>
<td>Feelings of shame rated as likely (%)</td>
<td>26.7</td>
<td>100.0</td>
<td>16.7</td>
<td>0.0</td>
<td>12.5</td>
<td>100.0</td>
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</table>
Chronic stress and HPA activation

Table 2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standardized mean difference (d)</th>
<th>k</th>
<th>SE_d</th>
<th>95% CI</th>
<th>p</th>
<th>Q_w</th>
<th>p</th>
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<tbody>
<tr>
<td>Cortisol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning samples</td>
<td>-.08</td>
<td>54</td>
<td>.03</td>
<td>-.14, -.03</td>
<td>&lt;.01</td>
<td>258.13</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Afternoon/evening samples</td>
<td>+.18</td>
<td>30</td>
<td>.04</td>
<td>+.09, +.26</td>
<td>&lt;.01</td>
<td>61.25</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Daily output</td>
<td>+.31</td>
<td>27</td>
<td>.05</td>
<td>+.20, +.41</td>
<td>&lt;.01</td>
<td>265.72</td>
<td>&lt;.01</td>
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<tr>
<td>Diurnal rhythm</td>
<td>+.39</td>
<td>4</td>
<td>.11</td>
<td>+.18, +.60</td>
<td>&lt;.01</td>
<td>4.99</td>
<td>&lt;.17</td>
</tr>
<tr>
<td>Post-DST sample</td>
<td>-.23</td>
<td>17</td>
<td>.09</td>
<td>-.40, -.07</td>
<td>&lt;.01</td>
<td>27.09</td>
<td>&lt;.04</td>
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<tr>
<td>Post-CRH sample</td>
<td>-.07</td>
<td>4</td>
<td>.18</td>
<td>-.41, +.28</td>
<td>&lt;.71</td>
<td>13.27</td>
<td>&lt;.01</td>
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<tr>
<td>ACTH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All samples</td>
<td>-.08</td>
<td>13</td>
<td>.09</td>
<td>-.25, +.10</td>
<td>&lt;.39</td>
<td>18.77</td>
<td>&lt;.10</td>
</tr>
<tr>
<td>Post-CRH sample</td>
<td>+.26</td>
<td>4</td>
<td>.17</td>
<td>-.09, +.60</td>
<td>&lt;.15</td>
<td>19.83</td>
<td>&lt;.01</td>
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<tr>
<td>CRH: All samples</td>
<td>+.66</td>
<td>3</td>
<td>.25</td>
<td>+.17, +1.16</td>
<td>&lt;.01</td>
<td>3.04</td>
<td>&lt;.22</td>
</tr>
<tr>
<td>GC receptor expression</td>
<td>+.03</td>
<td>4</td>
<td>.18</td>
<td>-.32, +.39</td>
<td>&lt;.86</td>
<td>38.92</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Note. Summaries are presented for outcomes assessed in three or more studies. Q_w is the heterogeneity statistic. CI = confidence interval; DST = dexamethasone suppression test; CRH = corticotropin releasing hormone; GC = glucocorticoid.

- most common HPA-indicator: morning cortisol
- Results:
  chronic stress --> disabled patterns of hormonal secretion. Lower cortisol levels in the morning, higher cortisol levels during rest of the day. CRH in cerebrospinal fluid is increased. ACTH levels remain the same.

Time since onset

- Greater time since onset associated with lower
  - total volume cortisol daytime
  - morning cortisol
  - ACTH
  - post-dexamethasone cortisol
Confirmation hypothesis:
chronic stress initially augments (vergroot) cortisol output, but is associated with a decreased output ‘below’ normal levels later on

Limitations

- Few prospective, longitudinal studies (chicken/egg)
- Overlap between trauma, controllability stressor, threat to physical integrity
- De-contextualization coding system: individual variability in controllability and key emotion. The studies have not considered individual differences in these factors.
- Additional moderating variables: developmental and genetic factors

Implications

- Implications of the increase in cortisol at first, but then the decrease to below ‘normal’ levels of cortisol
- First(early): hypercortisolism
  - atherosclerosis
  - insulin resistance
  - obesity
- osteoperosis
- excessive anxiety
- depression
- decreased immune function
- PTSD

Then(late): hypocortisolism:
- chronic fatigue syndrome
- irritable bowel syndrome
- auto-immune diseases (RA, allergy, PTSD)

Allostatic load and disease

➢ The allostatic load is "the wear and tear on the body" which grows over time when the individual is exposed to repeated or chronic stress. It represents the physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine response that results from repeated or chronic stress. The consequence is disease.

Cardiometabolic effects

➢ Effect of HPA-axis (dysregulation) on blood pressure, atherosclerosis, insulin resistance, abdominal fat --> risk factors for cardiovascular disease

➢ Measurement of allostatic load
  - cortisol
  - catecholamines
  - DHEA
  - systolic blood pressure
  - hip/waist ratio
  - blood glucose
  - cholesterol
--> very similar to symptoms of metabolic syndrome

Stress and health behavior

➢ Self reported stress is associated with
  - decreased physical activity
  - smoking behavior
  - increased risk of smoking
  - increased number of cigarettes
reduced self efficacy of quitting
reduced self efficacy of abstaining during stress
- increased intake of fatty foods

**Acute vs chronic stress**

- Cardiometabolic, behavioral and immune effects can be very adaptive in the short term
- Long term effects are not as adaptive
  - allostatic load --> cariometabolic effects
  - smoking, comfort food, reduced physical activity

**Remaining question**

- Where in HPA-axis is stress acting?
- Chronic stress: mainly effects on cortisol, not ACTH --> modulation at the level of adrenal cortex?
- GR feedback system < effective (shutdown problem)
- > production of CRF in amygdala as a result of cortisol feedback
- Sensitivity immune system to cortisol may decrease under conditions of chronic stress --> auto-immune diseases?
Class 4: Pre and perinatal stress: developmental origins of behavior, health and disease

TEXT

Developmental origins of health and disease (DOHaD)

- A person’s experience early in life affects his health throughout life
- Interdisciplinary research
- The association between unfavourable prenatal and perinatal life circumstances and later health and behavioral problems has been empirically proven --> but different interpretations. Underlying pathogenic mechanisms have not yet been discovered.
- Experimental manipulations on animals --> goal: understanding underlying cellular and molecular pathogenic mechanisms: “why do unfavourable early life experiences make an organism vulnerable for disease?”

Prenatal environment, health and behaviour

Do lifestyle diseases have their roots in prenatal life?

- Association between risk factors in pregnancy
  - high or low maternal weight
  - diabetes
  - endocrine disruptors
  --> often summarized in ‘birthweight’ and
  - obesity
  - diabetes II
  - cardiovascular diseases
  - cancers
  - increased stress sensitivity

First studies about low birthweight

- Low birth weight = indicator of disturbed foetal growth
- Barker hypothesis: birth weight associated with later diseases such as obesity, diabetes II and cardiovascular disease.
Criticism (methodological)

- Covariates (SES, life style factors, genetic factors,...) have not been taken into account.
- Methodologically improves studies have confirmed association between low birthweight and
  - cardiovascular disease
  - metabolic syndrome (obesity)
- Low birthweight + obesity --> highest chance of developing cardiovascular disease.
- Low birthweight and disease: not necessarily causal relation
  - low birthweight = indicator of unfavourable prenatal circumstances
  - unfavourable prenatal conditions can influence disease even when baby hasn’t got low birth weight
  --> mothers with low BMI: baby’s elevated risk of insuline resistance and high blood pressure
  --> mothers with high BMI: baby’s less sensitive to insuline and elevated risk for diabetes II
  --> administration of calcium: lower blood pressure
- Thus: low birth weight = ‘proxy’ measure (indirect measure) of variables we are truly interested in (unfavourable prenatal conditions)
- Research: It is best to use as many direct measures and response of baby as possible
- Clinical measures > ‘proxy’ measures:
  proxy measures do not show reciprocal relation (a-->b, b-->a), clinical measures do.
- No relation between unfavourable early life conditions and blood pressure at rest.
  Association between unfavourable early life conditions and blood pressure after exercise!
  Explanation: silent programming

Critical developmental periods

- Time during pregnancy that certain factor exerts influence = important.
  Not the same for all organs.
- Birth weight alone as predicting variable is not enough
- Long term effects on health depend on critical developmental periods (hungerwinter in Holland). Food shortage during
- first trimester --> cardiovascular disease
  breast cancer
  elevated stress sensitivity
  glucose intolerance
  altered blood coagulation (stolling)

- second trimester --> glucose intolerance
  microalbuminory
  airway pathology
  food allergy

- third trimester --> glucose intolerance

The thrifty (zuinig) phenotype

- Different hypotheses have been formulated to interpret disease in adulthood
  - the thrifty phenotype
  - the predictive adaptive response and subsequent mismatch between early and later environment-hypothesis

- Association between low birth weight and diabetes II
  explanation: thrifty phenotype?

- Diabetes II: insensitivity to insulin effects

- Thrifty phenotype hypothesis =
  foetus adapts to intra uterine food shortages --> insulin metabolism will be programmed ‘thrifty’ --> ‘thrifty’ phenotype. The foetus becomes resistant to insulin (removes excess glucose from blood) because it needs the sugar in the blood.
  Postnatal exposure to supernutrition --> thrifty phenotype can not act adequately
  --> diabetes II

- Limitations:
  - does not explain association between
  --> normal birth weight and later pathology
  --> high birth weight and later pathology
  --> weight increase during childhood and later pathology

Low birth weight: current situation

- Association between low birth weight and elevated risk for cardiovascular disease
  has been confirmed worldwide
- Low birth weight --> diabetes II: strong empirical evidence
- Low birth weight --> high blood pressure
  - already manifest during childhood
  - strength of association increases during age
- Birth weight ↘ then
  - ↗ osteoporose
  - ↗ polycystic ovarial syndrome
  - ↗ depression
  - ↗ schizophrenia
- Low birth weight --> functional somatic disorders (chronic fatigue syndrome, irritable bowel syndrome,...)???
  - few research
  - possible relation
  - indirect evidence: unfavourable early life conditions --> endocrine mechanisms (hypocortisolism) --> functional somatic disorders

**Conclusion**

- Low birth weight --> life style diseases: largely confirmed by methodologically improved studies
- Unfavourable early life conditions --> cardiovascular disease and obesity, also without an influence on birth weight
- Underlying mechanisms insufficiently known
  - programming?

**Prenatal origin of ADHD and other behavioral disorders**

**Prenatal stress and selfregulation**

- Maternal stress --> release of stress hormones (cortisol, adrenaline) --> influence on development foetus (programming on biological systems)
- Foetal programming on HPA-axis (not the only underlying mechanism)
- Glucocorticoids also have programming effect on prefrontal cortex and neurotransmitter systems
- Environmental factors, genetic factors and gene-environment interactions play a role
- Maternal negative emotions --> disturbed self regulation in later life
Effect of traumatic experiences

- Women who were pregnant during 9/11 and developed PTSD
  - babies had lower morning and evening cortisol levels than women without PTSD
  - babies stress response to new stimuli ↑ then cortisol ↓
- Other studies in same context:
  - lower birth weight

Long term prospective research

- Maternal stress + specific pregnancy anxiety --> baby
  - less able to adapt to new environment
  - difficult temperament
  - disturbed mental and motoric development
- Maternal stress -->
  - behavior problems
  - ADHD
  - sleeping problems
  - emotional problems
  - altered cortisol dayprofile
- High maternal cortisol levels --> baby high cortisol levels
  Subjective maternal stress --> baby high cortisol levels
- Objective stress (ice storm) --> general cognitive development impaired
  --> language development impaired
- Smoking --> ADHD

Our own prospective study

- Maternal anxiety explains 25 percent of the variance in foetal and neonatal movements and behaviors
  - High maternal anxiety --> more movement
    --> sleeping periods shorter
    --> more crying
    --> more sensitive
    --> more food-and sleep difficulties
    --> difficult temperament
- Maternal anxiety accounts for 22 percent of the variance in ADHD, 15 percent of externalizing problems and 9 percent of selfreported anxiety.
Maternal anxiety --&gt; flatter cortisol dayprofile: higher cortisol in the evening
Maternal anxiety --&gt; girls more depressed
Maternal anxiety --&gt; cognitive tasks:
- sufficient exogen response inhibition
- insufficient endogen response inhibition
- difficulty in integration and control of different parameters
- working memory, exogen inhibition and visual orientation/attention are intact

Possible explanation: subtile disruption in orbitofrontal cortex due to elevated levels of maternal cortisol.

Conclusion

Significant relation between maternal negative emotions and --&gt; disturbed emotional, cognitive and motoric regulation
U-formed relation: moderate level of maternal stress --&gt; superior mental and motory development:
--&gt; not enough research yet to confirm this hypothesis!!!
Relation between maternal stress --&gt; ADHD and externalizing problems stronger for boys
Relation between maternal stress --&gt; depression stronger for girls
Future: research that
- uses physiological measures for emotional, cognitive, behavioral effects
- includes genetic factors
  severity maternal negative emotions
timing maternal negative emotions
coping behavior mother

SUMMARY (slides)

Prenatal stress influences emotion, cognition and behavior regulation in later life
Maternal stress, anxiety, depression in pregnancy are significantly associated with (in infancy, childhood and adolescence)
- difficult temperament, high negative reactivity
- delayed behavioral development; e.g delayed self regulation
- ADHD problems, conduct disorders
- delayed cognitive development: ‘milestones’ e.g language
- specific cognitive deficits: neurocognitive tasks (inhibition)
- anxiety and depression
- changes in cortisol (HPA-axis)

-- 40 prospective studies using questionnaires, cognitive tasks, EEG, fMRI

- Examples of early life exposure reported to be associated with changes in emotion and cognition
  - maternal general anxiety or specific pregnancy anxiety
  - maternal daily hassles or important life events
  - maternal depression
  - partner of family discord (onenigheid)
  - intimate partner violence
  - distress caused by 6-day war in Israel
  - Experience of acute disasters: freezing storm, hurricane, 9/11

- ‘Prenatal stress’ vs ‘prenatal exposure to maternal stress’

‘Prenatal programming’: a concept with many faces

Plasticity during development

- Processes of proliferation, migration and differentiation are sensitive to intra-uterine conditions
- Plasticity during development (especially during critical periods) makes adaptation to prenatal environment possible: developing organisms absorb environmental information and adapt
- Risk: organisms adapts to infavourable prenatal conditions --> incorporation of these negative conditions --> structures do not develop well --> alterations in further growth, structure, physiology and metabolism of organs and systems
- (Negative) prenatal conditions --> programming influence on HPA-axis (but every organ and biological system can be influenced)
  = early life programming
- Early life programming contributes to the variability in (both normal and abnormal) behavior of people.

No clear meaning
‘Either the induction, deletion or impaired development of a permanent somatic structure or the “setting” of a physiological system by an early stimulus or insult operating at a sensitive period, resulting in long-term consequences for function.’

Programming influences all biological systems, such as
- HPA-axis
- sympathetic system
- CNS and neurotransmittersystems
- cardiovascular system
- immune system
- gastro-intestinal system
- renal system
- reproduction system
- musculoskeletal system

In literature, programming is often used in different, confusing terms

More than embryonal and foetal influence

Developmental processes not only during embryonal and foetal period, but also after birth. Prenatal and perinatal (10 weeks after birth) period = critial periods for neuronal development.

At birth: developmental processes not finished. Especially for
- brain
- teeth
- secondary sex characteristics
- cardiomyocytes (hartspiercellen)
- nefrones (niercellen)

Birth = important physiological adaptations to extra-uterine life, especially breathing

Diseases can be result of negative influences during embryonal and foetal periods alone --> e.g schizophrenia

Manifest and latent effects

Early life programming can result in manifest (visible) and latent (invisible) deviations
Silent programming: deviations are laten for many years
Elevated vulnerability of organism in both
Prenatal or postnatal stimulus --> vulnerable organism --> latent deviation becomes manifest.
- e.g low birth weigt --> blood pressure after exercise
Not deterministic but probabilistic

- Deterministic interpretation of prenatal/perinatal influences = wrong
- Epigenetic or other environmental influences also play a role in the development of an organism
- Evidence of prenatal/perinatal influences with manifest effects does not allow statements about potential changeability

Underlying mechanisms: growing research

- Defining a pathogenic mechanism = difficult
  why? Early life programming influences a multitude of biological systems
- Experimental research only possible by animal studies
- Epigenetic influences --> gen expression --> alterations in organs, tissues and homeostatic control systems
- See figure 5.1 in text
- Epigenetics: mechanism of inheritance without change in DNA-sequens of gen.
- Recent studies: mice: dietary differences influence colour of descendants
- Different underlying mechanisms in ‘early life programming’, but emphasis on
  - HPA-axis
  - endocrine system
  - oxidative stress
- Very great complexity of foetus’ systems (and their mutual interactions) that can be influenced by programming
- See figure 5.2 in text

Conclusion

- Growing research on relation of pre/perinatal conditions and health/behavior problems
- Unfavourable prenatal conditions are a risk factor for the development of
  - hypertension
  - diabetes
  - obesitas
  - cardiovascular disease
- Maternal negative emotions --> disturbed regulation of emotion, cognition and behavior + impaired development
  - ADHD
  - externalizing problems
- Underlying pathogenic mechanisms; experimental research on animals
- Critical developmental periods: organism incorporates information of the environment, inter alia through epigenic mechanisms.
- More research on epigenic mechanisms --> Insight in genesis of neurobiological vulnerability
- Lots of diseases have a genetic component which could be altered through epigenic mechanisms: future

SLIDES

- Exposure to adversity early in life can modulate developmental programming resulting in higher vulnerability for poor somatic and mental health outcomes across the life span

- What are the underlying mechanisms?
- Concept of development has changed: bidirectional processes: genes, behavior and environment; timing of interaction is important
- Early neural development:

  proliferation
  \[ \uparrow \quad \downarrow \]
  programming migration
  \[ \uparrow \quad \downarrow \]
  differentiation

  Brain at work during its construction!

- Genetic molecular cascades control development:

  - Many genes encode transcription factors that, in turn, induce the expression of other transcription factors, thus creating cascades of gene expression wherein a multistep signaling pathway results in amplification of the initial signal. This results in a high level of control over expression of the target gene or compound, all from a small initial signal.
  
  Within most differentiated cells, several levels of induction produce a multitude of transcription factors. Moreover, during embryonic development, the actual process of differentiation itself requires an integrated system of transcription factors that turn gene expression on and off with strict precision and timing.
  
  - see images in slides!
Epigenetics = the study of heritable changes in gene activity that are not caused by changes in the DNA sequence
- illustration:
  by chemical changes (e.g. DNA methylation) in chromatine, the DNA alphabet cannot be read. So, DNA sequens is unchanged (no mutation) but expression has changed.
  - mice experiment:
    epigenome = software (in addition, above)
    genome = harware (same in all cells)
    altered expression of genes in genetically identical mice
  --> Brown: DNA methylation (silenced agouti gene): healthy animal
  --> Yellow: no DNA-methylation (gene is expressed): sick animal (obesity, diabetes, cancer)

Brain development is from the beginning an interactive process. Environmental factors – not only mutations - can have an impact on later brain functioning during the whole period of brain development
- Prenatal exposure to maternal stress/anxiety:
  - disturbs the signalling pathways and alters expression of genes important for proliferation, migration differentiation of neurons in brain stem, hippocampus, amygdala, cerebral cortex --> affects brain development
  - Induces (subtle) irregularities in developing neurotransmitter systems, which can e.g change the balance in monoaminergic brain circuitries; changes brain-behavior relation (sensory system, motivation, reward)
  - Changes activity of immune cells in the brain: long term (re-)programming of the immune system
  - Changes the stress system; i.e HPA-axis and autonomic nervous system influencing reactions to stress: long term (re-)programming of the stress system
- Programming of HPA-axis:

- Maternal stress/anxiety/illness:
  - transplacental passage of cortisol?
  - correlation between maternal plasma and amniotic fluid cortisol levels during umbilical cord blood sampling = 0.43
  - programming of neurotransmitter systems?
  - programming of HPA-axis and ANS?
  - programming of immune system?
  - epigenetic changes observed in placenta and cord blood mononuclear cells

- Psychology and interdisciplinary research:
  - the effect of (induced) maternal negative emotions on fetal behavior

Induced maternal anxiety results in more general movements of the baby.
- Prenatal stress and reactivity to inoculation (inerting):
  high maternal cortisol: significant increase in infant cortisol after inoculation. Large variation at 15 minutes.
  --> a short small response after inoculation indicates better regulation than a large or prolonged response.
- Prenatal stress and cognitive functioning in adolescence:
  deficits in executive functioning (lateral prefrontal cortex)
- euroSTRESS: developmental programming by prenatal exposure to maternal stress
- PELS-study: modulation of developmental programming of cognition and emotion
  --> *Aim 1: (neuro)physiology and behavior*
  various types or prenatal life stress and their association with birth outcome, infant cognition, infant emotion
  ° Heart rate variability of women (during stress/during rest) --> sensory cognitive development?
  ° maternal anxiety --> differences in information processing?
    **EEG/ERP paradigm, results:**
    - ERP (event related potential) to standard sounds were larger in infants whose mother reported high anxiety during pregnancy.
    - prenatal exposure to maternal anxiety may affect the development of neural networks which lead to more extensive processing of sound with low information contents: do infants habituate less?
    - Is this vigilance/arousability inducing anxiety?
    - Altered auditory processing influence speech perception, language learning, dyslexia
  **Face processing: visual ERP’s at nine months:**
    - happy/angry, laughing/scared faces
    - discrimination
    - recognition
    - meaning
    - congruence V-A, incongruence V-A
    - crossmodality
  Results???

Future plans: follow-up
- examine how sensory-cognitive processes in infants develop (and relationship with prenatal anxiety of mothers) over time
- relate EEG/ERP differences to emotion and cognition temperament
- examine influence of “protective” factors on sensory-cognitive processes of offspring (over time)

Continuation of the follow-up studies on brain development:
Aim 2: (epi)genetics and behavior

Specific HPA-axis and placenta related genes and epigenetic changes x ‘ELS’ measures and their association with birth outcome, infant cognition, infant emotion

- Prenatal stress
  ↓
  changes in gene expression through epigenetic mechanisms
  ↓
  modifications of behavior and HPA-axis function

Functional candidate genes: HPA-axis (see slide)

- Prevention and intervention:
  Aims of this field of research = study early life stress
- fundamental research
- applied research
- mechanisms, processes typical/atypical development
- early prevention of mental health problems; interventions
  -- diagnosis earlier/adequate/accurate
  -- understand acquired vulnerability

- Programming ‘vulnerability phenotype’/stress diathesis/’double hit’ hypothesis:
Differential susceptibility:
Developmental programming: conclusion

Environmental factors in prenatal life
- influence developing brain areas and neuronal circuits
- have organizing effects (e.g. setpoints in systems)
- enhance adaptation to specific early environment:
  plasticity to adapt to other environments may be smaller

Behavior in postnatal life is affected by altered circuitry for
- sensory-cognitive functioning
- emotional functioning
- stress reactivity and regulation

Early adaptation may lead to problem behavior: match
Early adaptation may lead to optimal behavior: mismatch

Prenatal exposure to maternal anxiety, stress and depression modulates
developmental programming of the offspring

Epigenome and brain

We need
- more interdisciplinary research (DOBHaD)
- more longitudinal studies
- more intervention studies
- studies that look at potential benefits: create new paradigm; e.g. those that mimic ‘arousing’, ‘urgent’ situations (e.g. interactive games)
Class 5: Social factors in health and disease

SEE SLIDES

Text: Loneliness matters: a theoretical and empirical review of consequences and mechanisms

Abstract

- Loneliness
  - increased vigilance (waakzaamheid) for social threat
  - psychological processes
  - physiological functioning
  - increased morbidity and mortality

- Purpose paper: loneliness
  - what?
  - consequences?
  - theoretical framework (mechanisms?)

Introduction

- Loneliness = common experience
- U-shaped relation with age
- Loneliness = subjective social isolation
- Self reports
- Social disconnection motivates us to maintain and form social connections. This is necessary for the survival of our genes
- Chronic loneliness has serious consequences:
  - cognition
  - emotion
Loneliness matters for physical health and mortality

- Loneliness --> acceleration of physiological aging
  - cardiovascular health risk in young adulthood
  - increased systolic blood pressure
- Chronic loneliness has greater effects than situational loneliness
- Loneliness --> depression
  BUT loneliness continued to predict coronary heart disease, after controlling for depressive symptoms. Thus, depression is not a covariate.
- Loneliness --> increased risk for morbidity and mortality

Loneliness matters for mental health and cognitive functioning

- Loneliness associated with:
  - personality disorders and psychoses
  - suicide
  - increased risk for Alzheimer’s disease
  - diminished executive control
  - increased depressive symptoms
  - increased perceived stress
  - fear of negative evaluation
  - anxiety
  - anger
  - decreased optimism
  - decreased self esteem
  - cognitive decline
- Reciprocal relation between loneliness and depression
- Perceived sense of connectedness = scaffold (steiger) for the self
  = penetrates the physical organism and compromises the integrity of physical and mental health and well being
How loneliness matters: mechanisms

The loneliness model

- Perceived social isolation --> feeling unsafe --> hypervigilance for social threat --> cognitive biases --> negative social expectations --> confirming behavior from others
  - = self fulfilling prophecy
  - = self-reinforcing loneliness loop
- This loneliness loop is accompanied by feelings of hostility, stress, pessimism, anxiety and low self-esteem --> poor health outcomes

Health behaviors

- Loneliness and hypervigilance lead to diminished self regulation (automatic effects)
- Effortful attentional processes are impaired
- Self-regulation --> lifestyle behaviors
- Less self regulation --> less physical activity
- Loneliness = risk factor for
  - obesity
  - alcohol abuse
  - healthcompromising behavior
- Hypothesis: health behaviors have greater positive effect on socially connected people than on those who feel lonely

Sleep

- Sleep = physiological restoration
- ↓ sleep ↑ cardiovascular disease, inflammation, metabolic risk factors, hypertension, atherosclerosis, mortality
- Loneliness is associated with poor sleep quality and daytime dysfunction (low energy, fatigue).
- Loneliness is not associated with sleep duration
- Lonely feelings predict daytime dysfunction and daytime dysfunction exerts a small, but significant effect on lonely feelings (circle)
  Thus: the same amount of sleep is less salubrious (heilzaam) in lonely people and less salubrious sleep feeds forward to further lonely feelings
Physiological functioning

- Loneliness --> physiological functioning --> cardiovascular disease and mortality
- Long term loneliness is associated with elevated systolic blood pressure: association is stronger in older persons, suggesting an accelerated physiological decline in lonely vs non lonely people
- Loneliness --> elevated SBP --> cardiovascular disease
- But: do not forget lifestyle factors (diet, physical inactivity,...)

Neuroendocrine effects

- Loneliness correlates with greater concentration of epinephrine in overnight urine samples
- Dysregulation of the HPA-axis --> inflammatory processes that play a role in hypertension, atherosclerosis and coronary heart disease
- Loneliness is associated with higher levels of cortisol: prior-day feelings of loneliness, sadness, threat and lack of control --> higher cortisol awakening response. Cortisol awakening response does not predict physiological states later that day
- Loneliness leads to alterations of HPA-regulation, this occurs at the level of the gene

Gene effects

- Cortisol influences gene transcription
- Loneliness --> increased risk for inflammatory disease
  why? glucocorticoid insensitivity (evidence)
  = failure of the genome to “hear” the anti-inflammatory signal sent by circulating glucocorticoids
- Hypothesis:
  adverse social conditions (loneliness)
  ↓
  functional desensitization of the glucocorticoid receptor
  ↓
  altered gene expression
  ↓
  risk for inflammatory disease

Thus: loneliness exerts a unique transcriptional influence that has potential relevance for health.
Conclusion: impaired transcription of glucocorticoid response genes and increased activity of pro-inflammatory transcription control pathways provide a functional genomic explanation for elevated risk of inflammatory disease in individuals who experience chronically high levels of loneliness.

**Immune functioning**

- Loneliness --> impaired cellular immunity (lower natural killer cells)
- Additional research is needed to determine when and how loneliness operates to impair immune functioning

**Future loneliness matters**

**Interventions for loneliness**

1) Enhancing social skills
2) Providing social support
3) Increasing opportunities for social interaction
4) Addressing maladaptive social cognition

- Model of loneliness:
  Perceived social isolation --> feeling unsafe --> hypervigilance for social threat --> cognitive biases --> negative social expectations --> confirming behavior from others
  = self fulfilling prophecy
  = self-reinforcing loneliness loop
Thus, interventions that target social support, social skills, social access (=social cognitive therapy) are more effective (supported by research).

**Implications for health**

- Would a successful intervention to lower loneliness produce corresponding benefits in physiological mechanisms and physical health outcomes? NO
- Changes in loneliness are not responsible for improvements in health
- BUT criticism: the study that examined this used interventions that failed to address the hypervigilance and cognitive biases. This is crucial because the maladaptive social cognitions make loneliness the health risk factor it is
- More research is needed
Conclusions

- Human beings are thoroughly social creatures
- Loneliness is characterized by impairments in attention, cognition, affect, and behavior that take a toll on morbidity and mortality through their impact on genetic, neural, and hormonal mechanisms that evolved as part and parcel of what it means to be human
Class 6: Biopsychosocial aspects of dyspnea (breathlessness)

SEE SLIDES

Text: Anxiety, depression and panic

Introduction

➢ Anxiety, depression and panic are prevalent comorbidities in respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD)
➢ These negative affective states can impact the perception of dyspnea --> more negative outcome of the disease

Prevalence and impact of anxiety, depression and panic in asthma and COPD

➢ Comorbid psychological symptoms, especially
  - anxiety
  - depression
  - panic
  are highly prevalent in asthma and COPD
➢ Longitudinal studies have shown bidirectional influences between these comorbidities
➢ One respiratory disease and comorbid psychopathology are present; direct physiological and indirect behavioral pathways might mutually reinforce critical processes leading to a spiraling course of both diseases

Impact of anxiety, depression, and panic on the perception of dyspnea

➢ Positive relation between high levels of
  - anxiety
  - depression
  - panic
  - negative affect (also in healthy individuals)
  and perception of dyspnea
➢ Strong influence of negative affect on respiratory perception: evidence in studies manipulating short-lasting affective states (picture viewing):
  positive affective state --> less dyspnea perception
  negative affective state --> more dyspnea perception
  Also in healthy individuals!
Thus: the effect of affective states on respiratory perception might be a rather general phenomenon, not specifically depending on the chronic experience of respiratory symptoms.

Learning processes and context factors also influence dyspnea perception: experiment with ‘histamine challenge test’
--> the experience of asthmatic symptoms in a specific context may evoke the experience of similar symptoms when confronted with the context only

Repeated or chronic experience of dyspnea --> decreased perception of dyspnea (= habituation)

Negative affect reduces habituation to dyspnea (studies in healthy individuals)

High anxiety levels may prevent habituation to dyspnea or even induce sensitization to the unpleasantness of dyspnea. This can interfere with treatments or self-management of dyspnea. Exposure to repeated dyspnea in a controlled, safe setting (no anxiety) might reduce the unpleasantness of dyspnea.

Neural processes linking negative affectivity and perception of dyspnea

- Non invasive neuroimaging techniques allowed testing the following assumption:
  - limbic structures are involved in the processing of dyspnea (especially the affective dimension)

Studies using PET and fMRI

- Hypothesis: negative affective states and perception of dyspnea are integrated in the limbic and paralimbic areas
- Indirect support via fMRI-study (in healthy volunteers):
  - manipulation of affective unpleasantness of resistive load-induced dyspnea by affective picture viewing while keeping the sensory intensity of dyspnea constant
  - Results: increases in dyspnea unpleasantness involve activations of the anterior insular cortex and the amygdala
- Other fMRI study:
  - correlations between unpleasantness ratings for resistive load-induced dyspnea and activations of the anterior insula and the ACC
- Study with patients with stroke lesions of the insular cortex:
  - Patients showed reduced perceptual sensitivity for resistive load-induced dyspnea and also for cold pressure pain. Important: more so for the unpleasantness than for the actual intensity
Another fMRI-study: compared resistive load-induced dyspnea and heat pain in healthy volunteers. Results: Perception of both aversive sensations is partly processed in similar brain areas, including:
- insula
- ACC
- amygdala
- medial thalamus
--> they all play a role in the processing of negative affectivity.

Conclusion: these findings suggest that a common affect-related human brain network underlies the perception, upregulation and downregulation of different aversive bodily sensations, including dyspnea.

But: studies used healthy individuals (indirect evidence). No definitive conclusions.

Studies with patients with airway diseases:
- longer disease duration was correlated with greater reduction in insular cortex responses, which might represent a neural habituation mechanism reducing the affective unpleasantness of dyspnea over the course of the disease.
- affective aspects of dyspnea on the functional as well as structural neural level might be processed in a specific manner in patients with asthma, which is related to disease duration.
- it appears that the PAG is an important neural region for controlling affective respiratory responses.

Studies using respiratory-related evoked potentials (RREP’s):

- RREP elicited by short inspiratory occlusions (afsluitingen)
- Examination of effects of transient affective states elicited by viewing pleasant, neutral and unpleasant picture series on the RREP
- Results: reduced P3 amplitudes (less cognitive processing) for inspiratory occlusions presented during pleasant or unpleasant series, when compared to those presented during neutral series.
--> Hypothesis: emotion impacts the perception of respiratory sensations by reducing the attentional resources available for the neural processing of afferent respiratory sensory signals.

But: perceived intensity was higher during the unpleasant picture series.
--> Speculation: the perception of the respiratory sensation becomes more dependent on parallel emotional arousal than on the neural processing of the stimulus.
Another study: compared RREP’s in low and high state anxious individuals:
low anxious --> less cognitive processing
high anxious --> more cognitive processing
These results support on a neural level previous findings showing increased perception of respiratory sensations in high anxious individuals, especially in unpleasant vs neutral/pleasant emotional contexts.

A further study: examined neural processing of respiratory sensations when breathing itself changes its affective value and becomes more difficult and unpleasant during sustained breathing through an inspiratory resistive load.
--> Findings suggest that when breathing becomes more difficult and unpleasant (and thus motivationally relevant), sensations from the respiratory system demand greater attentional and neural resources.

Two further studies in healthy individuals: used the RREP to examine the influence of anxiety on sensory gating (filtering out unnecessary stimuli).
Results: individuals with high anxiety show reduced respiratory sensory gating and increased afferent input to cognitive brain centers.

These interactions between negative affect and neural processing of respiratory sensations might be related to an overperception of dyspnea in vulnerable individuals.

Rest of text is not mentioned in slides.
Class 7: Emotions, stress and asthma

SLIDES
Text: Airway responsiveness to psychological processes in asthma and health

ABSTRACT

- Psychosocial have been found to impact airway pathophysiology
- Goal of this article:
  1) airway responses to psychological stimulation
  2) pathways of influence
  3) present an emotion-induction paradigm

EFFECTS OF PSYCHOLOGICAL PROCESSES ON THE AIRWAYS – EARLY OBSERVATIONS AND FINDINGS FROM PATIENTS’ REPORTS

- Faulkner: esophagus, diaphragm and bronchial passages contract with unpleasant stimulation
- Dekker and Groen: asthma patients: stimuli = memories of highly emotional episodes of their lives → dyspnea and lung function decline
- Smith et al: induction of negative emotions through hypnosis:
  --> increases in total pulmonary resistance
- These reports are supported, but there is no such thing as a purely “psychogenic asthma”
- Thus: responding of the airways to psychological stimuli is more a dimensional phenomenon, with some susceptible patients experiencing stress and emotions as predominant factors, others more as subordinate (ondergeschikt) factors
- Important motivation for research: studying actual airway function in response to psychological stimuli

OBSERVATIONAL STUDIES ON AIRWAY RESPONSES TO PSYCHOLOGICAL STATES

- systematic observational studies have confirmed an association between emotional states, mood, or stress and changes in spirometric lung function
- Negative mood states are associated with reduces lung function
  But: individual differences!
- Different types of stress → very different associations:
  - negative effect over 3 month period: decreased exhaled air (FEV1)
  - daily hassles: increased exhaled air (FEV1)
  --> these changes were mediated by changes in airway inflammation (FeNO)
- Laughing --> 30 à 50 procent report airway constriction
- Crying --> 40 procent report asthma symptoms of wheezing/coughing
- Rollercoaster ride --> reduction in lung function in women with asthma, but not in healthy controls

PSYCHOLOGICAL STIMULATION UNDER CONTROLLED CONDITIONS: EXPERIMENTAL SUGGESTIONS ALTER BRONCHOMOTOR TONE

- the bronchoconstrictive suggestion paradigm: participant is required to breathe through a mouthpiece from a canister (which is introduced as containing a powerful bronchoconstrictor substance):  
  Results: airway obstruction of a clinically relevant size (20 à 40 percent of asthma patients). Also in participants without lung disease.  
  Measurement: respiratory resistance is measured by the forced oscillation technique (FOT)  
  Likely mechanism: vagal pathway
- Providing bronchodilatory suggestions alone: mixed results  
  the exact relationship of the suggestion paradigm remains unclear

MODIFICATION OF AIRWAY RESPONSE TO PHYSICAL, PHARMACOLOGICAL, AND ALLERGIC STIMULI BY PSYCHOLOGICAL FACTORS

- A number of studies have demonstrated modification of airway hyperreactivity by psychological factors
- Luparello et al:  
  - presenting a bronchodilator as a bronchoconstrictor reduced its bronchodilatory effect.  
  - hypnotic suggestions of relaxation, well-being, and exercise without breathing difficulty reduces the size of the bronchoconstrictor response  
  - patients with exercise-induces asthma: those who had repeatedly experienced symptom relief by pre-exercise inhaler use are more likely to show less exercise-induced obstruction when subsequently administered a placebo inhaler
- Allergen-induced airway responses:  
  a slight attenuation (verzachting) of FEV1 (exhaled air) decline (thus more exhaled air) when inhalation of the allergen was followed by a recall of stressful life situations
Pleasant hypnotic suggestions and mood attenuate the immediate hypersensitivity response of the skin to histamine

A variety of mechanisms can probably account for these different instances of psychological modulation or airway hyperresponsiveness

AIRWAY RESPONSE TO LABORATORY EMOTION-AND STRESS-INDUCTION

With relative consistency, findings suggest a decrease in spirometric lung function or increase in respiratory or airway resistance during negative affective states

Some studies also suggest that eliciting positive emotional states leads to airways constriction

Constriction in the central airways is probably the main source of emotion-induced resistance increases, with little contribution by changes in compliance of the airways

Overall, surgery films elicit the strongest airway constriction across subjects

Induction of emotions by other techniques has generally confirmed findings with film induction, although effects may be weaker

Laboratory stress tasks have less consistent findings

Further studies found evidence for bronchodilation or bronchoconstriction in both healthy and asthmatic participants

Summary:
emotional stimulation induces mild airway constriction under laboratory conditions. Effects are strongest for unpleasant stimulation material, particularly blood and injury-related films. Positive emotional material has also shown effect in some studies. Constriction appears to be a general response characteristic of the airways to this type of stimulus material regardless of disease status, although some studies have shown stronger effects in asthma patients. Findings with stressful stimuli have remained less consistent.

METHODOLOGICAL ISSUES IN STUDIES OF STRESS-AND EMOTION-EFFECTS ON THE AIRWAYS

Some inconsistencies remain, in particular in the stress-induction literature
Measurement technique

- Forced expiratory maneuvers:
  - only provide indirect measures
  - may enhance bronchoconstriction by irritation of the airways
  - may dilate the airways through deep inhalation
  - subject to multiple psychological influences (attention, effort)
- Respiratory resistance monitoring:
  - direct measure
  - more valid results

Timing of assessments

- Measurements are too far removed (before/after test) from the psychological phenomenon of interest; the resistance change elicited by an emotional state
- This is a problem because an emotional state cannot be expected to continue after task offset (especially in the laboratory setting). Recovery from the emotional state will be measured
- Continuous assessment of lung function is time consuming and distracting the participant from his task

Quality and intensity of the psychological state elicited

- It would be simplistic to expect that many different psychological states lead to the same outcome in terms of responding of the airways.
  - but: induction of a variety of emotions has been associated with bronchoconstriction
- Quality of unpleasant affective states:
  - passive coping tasks (picture viewing) --> bronchoconstriction
  - stress tasks --> counteract bronchoconstriction
  - Emotional quality of both tasks is different, therefore they are not comparable
- Intensity of the elicited state can also determine airway constriction:
  - stronger respiratory resistance increase in blood-injection-injury phobia individuals
- Hypnotic suggestion tasks have elicited bronchoconstriction or bronchodilation:
  - but: individual differences in susceptibility to suggestion
- Note: the character of the employed stress challenges has been acute.
  - There is little consensus on exact definition of acute vs chronic stress challenges
Monitoring of manipulation success (how well are experimental studies conducted?)

- Uniform responding to experimental induced emotions cannot be expected
- The psychological assessment side is unsophisticated. There is no use of self-reports for example
- None of the descriptions can serve as a validation or ultimate indicator for the presence or absence of emotion
- At the minimum, inclusion of the experiential level would serve as an additional indicator (how does the participant experience the emotion-inducing stimulus?)

MECHANISMS OF EMOTION-INDUCED AIRWAY CONSTRICTION

- A variety of underlying mechanisms has been proposed for psychologically induced airway constriction
- Things to keep in mind:
  - heterogeneity in physiological activity
  - multiple pathways --> same outcome?
  - Different forms of psychologically-induced airway constriction

Autonomic pathways

- Best evidence comes from laboratory studies using pharmacological blockade
- Cholinergic pathway = main bronchoconstrictor
- Central vagal excitation or altered sensitivity to normal vagal outflow at the end-organ level = possible mechanism
- Centrally mediated vagal excitation can only be viewed as a major pathway of bronchoconstrictive suggestion effects if airway hyperreactivity to these pharmacological challenges itself is also viewed as at least partially mediated by central vagal pathways
- Central vagal excitation appears to be the critical final pathway linking psychological processes to airway responses to viewing of emotional film and picture stimuli
- The positive association between an index of sympathetic excitation and respiratory resistance defies simple interpretations and it is unclear whether it
  - signifies an instance of autonomic nervous system fractionation (breking)
  - is a sign of a more widespread damage to cholinergic neurotransmission by allergic processes
  - only constitutes a correlation of processes that are functionally unrelated but associated through their relationship with an unknown third variable
Other autonomic pathways, such as the nonadrenergic-noncholinergic system have not yet been studies in humans:
- mice: sensitized and allergen challenged mice --> stronger airway hyperreactivity
- As a hypothetical pathway, stress could enhance activity of the HPA-axis, which has been shown to raise nerve growth factor levels, and that in turn may induce substance P secretion (causes bronchoconstriction) in the airway epithelium
- General problem with studying autonomic pathways:
  There is a considerable amount of target organ specificity. Indices of autonomic functioning derived from other organ sites cannot necessarily be expected to inform about autonomic regulation of the airways

Endocrine changes
- Research in the context of stress and emotion effects on the airways is still in its infancy

Ventilatory changes
- Ventilatory changes are known to influence airway smooth muscle tone in a number of ways:
  - deep inspiration --> bronchodilation
  - ↑ functional residual capacity --> bronchodilation
  - hypocapnia --> bronchoconstriction (stronger effect in asthma patients)
  - hyperventilation --> bronchoconstriction
  How? Through drying/cooling of the airways = major pathway of exercise-induced bronchoconstriction
- Given that ventilatory influences have often been suspected as a major pathway in emotion-induced airway responding, surprisingly few studies have been conducted
- In emotion-induction studies:
  - ventilatory changes are not consistently related to changes in respiratory resistance
- Ventilatory influences could me most prominent in states involving marked emotional expressions (crying/laughing)
- In addition to drying/cooling, stimulation of irritant receptors through high flow rates could be another mechanism
CNS pathways of emotion-induced airway constriction

- Animal studies:
  Vagal neurons constitute the central integrators of multiple CNS influences on airway smooth muscle tone
- Input is provided from higher CNS centers
- PAG = area with central role.
  Activation of the PAG --> smooth muscle relaxation
- PAG: 2 pathways:
  1) GABAergic inhibitory pathway
  2) hypothalamus -> vagal neurons (activity is increased)
- Amygdala --> paraventricular nucleus: a pathway for inducing bronchoconstriction by negative emotions
- Little is known about relevant brain regions in humans:
  - activation of the PAG --> reduced dyspnea perception
  - bigger PAG --> longer duration of asthmatic disease
  - stimulation of PAG --> improvements in some aspects of spirometric lung function
- Taken together with findings from animal research, PAG functioning may have a central role in mediating emotion-induced airway responses
- Exploring brain regions linked to emotion-induced airway constriction will also require careful consideration of neural pathways involved in ventilatory responses to emotion, which will most likely show a certain degree of overlap
- Environmental exposure and disease states of the airways may impact vagal preganglionic neurons or pathways that connect with them and may thus alter CNS processing of various stimuli including those of a psychological character.
  - allergen exposure --> bronchoconstriction
- To date, studies linking CNS pathways with airway responses to emotional stimuli are missing
- Inflammatory processes in the airways (as a reaction to allergens) have also been shown to be associated with brain responses to asthma-related compared to neutral words --> reflects awareness of inflammatory condition
Airway immune and inflammatory pathways of emotion-induced airway constriction

➢ Important role of stress and emotion in modulating systemic markers of inflammation in asthma
➢ Dominant paradigm: capacity of stress to modulate allergic responses by stimulation of white blood cells
➢ Observational research:
  - acute negative affect --> reduction in FEV1 (exhaled air)
  - daily hassles across 3 months --> improvements in FEV1
  --> these associations were mediated by FeNO (measure of inflammation)
➢ It is possible that negative emotion-induced airway constriction is based more on phasic change in autonomic outflow, whereas current negative affect as a mood state leads to more tonic (inhibitory) change in inflammatory parameters that may also affect the airways
➢ Underlying mechanisms in phasic component: mast cells that release bronchoconstrictive mediators
  But: the role of early-phase response inflammatory mediators (secreted from mast cells) deserves further scrutiny (kritisch onderzoek) as a pathway affecting airway tone in acute stress
➢ Nitric oxide --> either bronchodilation or bronchoconstriction depending on its source. Further research is needed!

➢ Summary:
At the present stage of research, the two most plausible pathways linking emotion or stress with bronchoconstriction are autonomic vagal and ventilatory influences (in particular airway cooling/drying). It should be noted that these pathways would likely result in different temporal characteristics of bronchoconstriction (figure 2).
Vagally mediated responses have a fast onset, gradually decay throughout emotional stimulation, and subside (nemen af) within 1-2 min following stimulus off-set.
Hypothesized airway responses mediated by ventilatory changes (such as hyperpnea), would follow a similar trajectory as bronchoconstriction induced by exercise-or cold air hyperventilation- with a delayed onset during the late phase of a longer emotional stimulation or after off-set of stimulation and persistence of constriction over 20-40 min.
So far, only empirical evidence for the first type of response trajectory!
CLINICAL RELEVANCE OF EMOTION-INDUCED AIRWAY OBSTRUCTION

- Indicators of importance?
  - overall intensity of constriction
  - association with asthma-related symptoms
  - association with patients’ experience of emotion-induced asthma symptoms
  - airway obstruction in daily life

THE FILM PARADIGM FOR ELICITING EMOTION-INDUCED AIRWAY OBSTRUCTION

RECOMMENDATIONS

not mentioned in slides

CONCLUSION AND OUTLOOK

- Psychologically elicited airway responses have been well described in the literature and can be elicited with standardized laboratory challenges
- There is a growing realization that psychosocial factors influence the pathophysiology of the airways in asthma
- Vagally mediated airway constriction that accompanies affective processes may play a central role in this context
Class 8: Pain
SLIDES

Text: The fear-avoidance model of musculoskeletal pain: current state of scientific evidence

INTRODUCTION

Fear and anxiety: a brief introduction

- Fear is the emotional reaction to a specific, identifiable and immediate threat
- Anxiety, in contrast to fear, is a future-oriented affective state and the source of threat is more elusive (ontsnappend) without a clear focus
- Fear --> motivates the individual to engage in defensive behaviors
  Anxiety --> associated with pretentive behaviors, including avoidance
- Both avoidance behavior and hypervigilance reduce anxiety in the short term, but may be counterproductive in the long run

FEAR AND PAIN

- Pain-related fear and anxiety = fear that emerges when stimuli that are related to pain are perceived as a main threat
- Fear and anxiety response: compromises physiological (e.g. heightened muscle reactivity), behavioral (e.g. escape and avoidance behavior) as well as cognitive elements (e.g. catastrophizing thoughts)

The fear avoidance model of pain

- = a cognitive behavioral model of CLBP (chronic lower back pain)
- Basic tenet: the way in which pain is interpreted may lead to two different pathways (see figure 1)
  ➔ Pathway 1: acute pain is perceived as non-threatening --> functional recovery
  ➔ Pathway 2: pain is catastrophically misinterpreted --> pain-related fear and safety seeking behaviors --> vicious circle
The fear avoidance model of pain: evidence for its components

Pain severity

- Numerous studies have shown that pain intensity has a considerable contribution in explaining disability
- It can be concluded that the association between pain and disability both during the acute and chronic stages of pain may be more important than previously suggested

Pain catastrophizing

- = the process during which pain is interpreted as being extremely threatening
- Pain catastrophizing has consistently been associated with pain disability in pain patients as well as in the general population
- Pain catastrophizing may be related to intensified pain in various pain problems
- Experiment: manipulation of the meaning of a painful stimulus. What is its effect on the pain experience?
  - healthy volunteers who were told a cold metal bar was hot, rated it as more painful and damaging than participants who were led to believe that the same bar was cold.
  - the damaging interpretation mediated the relationship between the experimental manipulation and the pain experienced.
- Pain catastrophizing may be a precursor of pain-related fear

Attention to pain

- Various studies have demonstrated that excessive attention to pain is dependent upon the presence of pain-related fear
  - decreased cognitive task performance in fearful LBP patients (they direct their attention to pain)
- Pain-related fear --> Pain vigilance
  - diminished attentional bias due to treatment
- Pain-related fear and pain vigilance seem to contribute independently to the experience of pain
- Attentional disruption by pain-related information is not the result of an initial shift of attention to the pain stimuli, but rather stems from difficulties in disengaging (losmaken) attention from these stimuli
  - high pain catastrophizers had more difficulty in disengaging their attention from pain cues than low catastrophizers
- It may be that attentional engagement is facilitated by the anticipation of pain
In sum: there is evidence that attention may be an important feature in pain perception as predicted by the model

Escape/avoidance behavior

- Avoidance refers to behavior aimed at postponing or preventing an aversive situation from occurring
- Avoidance behavior might be reflected in submaximal performance of activities (abstinence from physical activity)
- Studies: fear-avoidance beliefs were related to diminished physical task performance

Disability

- Disability refers to problems in executing daily life tasks and activities
- Disability may be a logical consequence of prolonged avoidance behavior and hypervigilance
- CBLP patients with heightened levels of pain-related fear report increased disability

Disuse

- The term “disuse syndrome” refers to the physiological and psychological effects of a reduced level of physical activity in daily life
- Two aspects of disuse seem relevant
  1) physical deconditioning: measured by aerobic fitness levels
     - the physical fitness of CLBP patients is found to be either low or equal to that of healthy subjects
  2) disturbed trunk muscle coordination: no clear results
- In sum: neither lower physical activity levels nor the physical consequences of long-term avoidance behavior in CLBP patients were unambiguously confirmed

Vulnerabilities

- Are there certain vulnerabilities that predispose individuals to overly attach negative appraisals to pain?
- There is evidence that pain-related fear is related to
  - anxiety sensitivity
  - injury/illness sensitivity
  --> trait anxiety
Interrelated hierarchy:

- general negative affectivity
  - specific anxiety sensitivity and fear of pain

- It may be (speculative) that individuals with an increased vulnerability to catastrophizing and pain-related fear are less changeable in their fear beliefs

- Pain catastrophizing and pain-related fear mediate the relationship between neuroticism and pain vigilance, and that pain vigilance is associated with heightened pain severity

- Neuroticism moderates the relationship between pain severity and pain catastrophizing

- Pain catastrophizing is related to
  - pain-related fear
  - depression
  - disability

- Both depression and disability are related to pain severity

- No causal inferences can be made, but these studies do support the associations between various elements of the fear-avoidance model

PAIN-RELATED FEAR DURING VARIOUS STAGES OF LOWER BACK PAIN (LBP)

Pain-related fear as a maintaining factor of CLBP

- One of the key mechanisms in the maintenance of anxiety disorders are safety and avoidance behaviors

- Fearful pain patients may continuously scan their environment for potential signs of pain, and when the detected stimuli are perceived as a threat, the attention is more likely to stay attached to those stimuli

  --> less attention available for other tasks and activities

  --> intensified pain

  Thus disrupted attentional processes are associated with increased disability because of these relations

- Avoidance behavior fuels the pain-related fear

- Escape/avoidance behavior and disrupted attentional processes may therefore contribute to the maintenance of CLBP
Pain-related fear as a risk factor for the development of chronic LBP

- Due to its associations with escape/avoidance behavior already during the acute pain phase, pain-related fear might contribute to the development of a chronic pain problem.

Pain-related fear as a vulnerability factor for the inception (begin) of acute LBP

- Recent studies demonstrated fear avoidance beliefs to be present in pain-free people.
- These fear avoidance beliefs may act as a vulnerability factor.
- Fearful people may be more inclined to misinterpret ambiguous physical sensations as threatening or painful, and therefore have an increased likelihood to experience pain.
- There is indeed some evidence that fear avoidance beliefs may heighten the probability of subsequently developing a new pain episode.

PAIN RELATED FEAR AND TREATMENT

- The previous findings suggest that pain-related fear may not only be associated with the inception of a LBP episode, but also with the transition from acute to chronic lower back pain, and the maintenance of a chronic pain problem.

Pain-related fear: an impeding (belemmerend) factor of treatment?

- A working alliance is of importance for positive treatment progress.
- More research is required to investigate whether pain-related fear actually impedes the patient-therapist relationship.
- Patients pain-related fear may be fed by the interaction with health care providers:
- 
  - diagnostic terms
  - health care providers may have fear avoidance beliefs themselves (can induce or strengthen those of their patients, especially the fearful ones)
- It is not clear whether fearful CLBP patients can benefit optimally from traditional health care
- 
  - patients may respond with more safety and avoidance behaviors to these treatments.
Effectiveness of cognitive behavioral programs

- They address pain-related fear
- These programs have demonstrated promising results, indicating that it can be beneficial to focus on decreasing pain-related fear
- It might be that the presence of fear avoidance beliefs debilitate (verzwakken) outcome when usual treatment is applied, whereas fear-avoidance based treatments fail to be effective in the absence of pain-related fear
- The effectiveness of these programs in reducing disability was associated with decreases in
  - pain catastrophizing
  - pain-related fear
- Thus:
  these results suggest that cognitive behavioral programs, and even brief educational sessions, can effectively diminish disability, which might be due to reducing fear avoidance beliefs and pain catastrophizing.
  Pain-related fear might therefore be an essential target for successful interventions

Exposure in vivo

- Developed to gradually confront patients with activities they feared and avoided due to fear avoidance beliefs
- Four components:
  1) the choice of functional goals
  2) education about the paradoxical effects of safety behaviors
  3) the establishment of a fear hierarchy
  4) graded exposure to feared activities in the form of behavioral experiments
- This treatment may provide patients with the most convincing evidence that expected harmful consequences of these feared activities are in fact an overestimation.
  --> their fear may diminish and functional abilities might be promoted
- Several experiments have demonstrated the effectiveness of “exposure in vivo” as compared to graded activity in fearful CLBP patients, by reporting impressive reductions in pain-related fear and disability, as well as increases in activity levels in the home situation
- These studies provide support for extending generalization of “exposure in vivo” treatment across settings and therapists
The educational part also produced improvements:
- ↓ pain-related fear
- ↓ catastrophizing

Measures of actual behavior improved after the exposure settings, not after the educational sessions

Resumption of daily activities in patients was associated with decreases in pain-related fear, but NOT with a reduction in pain-intensity

**Generalization of “exposure in vivo”**

- Important assumption behind exposure in vivo:
  the repeated experiences of being able to perform various activities without pain during treatment will extend to activities during daily life
- But:
  findings say that generalization of these corrective encounters is limited in chronic pain patients:
  - effect failed to generalize to other dissimilar movements (that were not part of treatment)
  - patients learn an exception to the rule “activities hurt”, rather than to change their fear avoidance beliefs
- Interestingly, these patients tended to overgeneralize pain (once a movements hurts, it will always hurt in the future)
- Future research: investigate whether the overprediction of injury is as difficult to generalize to dissimilar movements as the overprediction of pain
- Treatment implications:
  - importance of practicing a wide variety of activities and movements, also in the home environment
  - adding cognitive techniques
- It can be suggested that the addition of behavioral experiments optimize generalization of corrective encounters

**CONCLUSION AND UNEXPLORED ISSUES**

- There is support for the fear-avoidance model
- Pain-related fear is associated with:
  - misinterpretations of pain
  - hypervigilance
  - ↑ escape and avoidance behaviors
Disrupted attentional processes + avoidance behavior were found in fearful CLBP
Less evidence for the existence of disuse (measured by aerobic fitness level)
Pain severity plays an important role in disability
Several personal vulnerabilities (fundamental fear, neuroticism) may influence whether someone will respond fearfully to a painful experience
Pain-related fear may
- vulnerability to develop new LBP episodes in currently pain-free people
- risk for continuation of LBP complaints and may maintain complaints when they have become chronic
But: Prudence! Individual differences also account for outcomes. It is not so that once patients respond with pain-related fear to pain, they will inevitably become mired in a vicious circle.
Also important: the fear-avoidance model only accounts for a subgroup of CLBP patients; various other factors may play a role
The fear-avoidance model does not provide evidence for causal interrelationships
Future research: interesting remaining issues (see below)

Pain-related fear: when is it adaptive and when dysfunctional?

- Difficult: lack of objective measures of what is adaptive
- One approach: contextual issues, e.g. is there real harm? Consequences on function and identity?
- Acute stages of pain:
  pain-related fear is adaptive --> direct attention towards the injury --> necessary care
- Enduring pain:
  pain-related fear is dysfunctional: persevering use of avoidance and escape behaviors
- Thus: pain-related fear is never dysfunctional, but it is the prolonged engagement in safety behaviors that is dysfunctional

When to target pain-related fear?
Prevention!
- preventing dysfunctional reactions when a new pain episode is initiated
  - educational campaigns (but, does changing fear-avoidance beliefs lead to actual behavioral change?)
- prevention of development of enduring pain once an acute LBP episode is established (identification of those at risk)
- Target risk factors; thereby putting harmful developmental processes in pain on hold

**Pain-related fear in patients with specific pain diagnoses**

- There is every reason to believe that fear processes would be applicable to specific pain problems as well

**The object of fear**

- Fear of pain and avoidance behaviors may not be the only kind of fear associated with chronic pain
- Another important concern may be social isolation that occurs in response to less participation in daily life
- It may be that concerns about social isolation in pain patients increase their pain threshold
- Carver and Sheier’s goal-oriented model of self-regulation:
  - Approach goals: goals that the individual is hoping for
  - Avoidance goals: situations that have a negative value
  Fear = emotional reaction to a movements towards an avoidance goal
  Thus: chronic pain may induce fear
  Research efforts have just started

**Task persistence instead of avoidance**

- Fear is not always associated with avoidance behavior, sometimes persistence
- Mood-as-input model:
  predicts that task performance is the result of the interaction between mood and certain stop rules. If “as many as possible” stop rule --> negative mood will facilitate task performance, positive mood will inhibit task performance
- Awaits further investigation
ABSTRACT

- 1) overview of studies that demonstrate an association between functional dyspepsia and psychological traits, states or psychiatric disorders
- 2) How do psychosocial factors and psychiatric disorder exert their role in functional dyspepsia? Pathophysiological evidence. Brain imaging studies!
- An integrated model of functional dyspepsia as a disorder of gut-brain signalling = biopsychosocial approach

INTRODUCTION

- Psychological processes have been linked to upper abdominal symptoms or presumed gastric origin for decades
- Little has changed in modern times in both the symptom-based nature of the definition of functional dyspepsia and the key issues regarding the association between psychopathology and gastric symptoms

EPIDEMIOLOGY

Psychopathology and functional dyspepsia

- Generally, the vast majority of studies point towards higher levels of psychopathology in patients with functional dyspepsia than in healthy controls. The evidence is the strongest for anxiety, depression and somatization
- Meta-analysis 2003: Association between anxiety, depression and functional dyspepsia
- Personality traits and functional dyspepsia --> mixed results
  Functional dyspepsia does not seem to be associated with a particular personality profile, although increased levels of neuroticism have been found
- Koloski et al: a higher prevalence of physical and emotional abuse, but not other forms of abuse
- Studies on stressful life events suggest some divergence on the number of stressful life events in patients with functional dyspepsia
Functional dyspepsia is associated with panic disorder

**Aetiological (origin of something) importance of psychopathology**

- Debate: Is psychopathology a feature of functional dyspepsia as such or is it merely driving health-care-seeking behavior?
- Two lines of evidence have strengthened the case of a central role of psychological morbidity, beyond or in addition to its influence on health-care-seeking behavior
- Studies: higher levels of psychological morbidity in patients with functional dyspepsia than in nondyspeptic controls
- Other studies: psychological morbidity is not strongly related to health-care-seeking behavior in functional dyspepsia, other factors (abdominal pain) are far more important
- Thus: psychological morbidity might influence functional dyspepsia pathophysiology or symptoms **directly**, in addition to its potential influence on health-care-seeking behavior
- But: studies do not enable causality conclusions
- Koloski et al 2012: demonstrated that in individuals without dyspepsia symptoms at baseline, anxiety predicted dyspepsia symptoms at follow-up. No reciprocal relation!
  A few other studies point in the same direction.
- Taken together, these emerging studies provide some preliminary evidence for a role of psychopathology in the aetiopathogenesis (initiation) of functional dyspepsia, rather than merely being the consequence of (chronic) somatic symptom burden
- Two noteworthy studies on psychological treatment: Intensified medical groups (+cognitive behavioral therapy, relaxation therapy,...) showed increased improvement of dyspepsia symptoms and health-related quality of life
Psychopathology and dyspepsia symptom severity

- Monitoring --> increased perceived symptom severity
- Emotional support and flexibility --> reduced symptom levels
  But: the beneficial role of emotional support is present only among those with increased coping flexibility
- Psychological factors, especially somatization, correlate with most functional dyspepsia symptoms
- Depression and somatization are the two most important factors (effect of depression is partly mediated by somatization)
- Rome III subdivision of functional dyspepsia into
  - epigastric pain syndrome (EPS)
  - postprandial distress syndrome (PDS)
- Somatization was associated with all three symptom factors, whereas depression was only associated with PDS

Psychopathology and quality of life

- Severe impairment in both physical and mental aspects of quality of life have been consistently reported
- In addition, abuse history and psychiatric comorbidity influence both physical and mental aspects.
  The influence on physical aspects might be mediated by somatization

Gastric sensorimotor dysfunction

- Gastric sensorimotor dysfunction is associated with functional dyspepsia
- Psychosocial factors and/or psychiatric disorders and gastric sensorimotor dysfunction interact in symptom generation
- High stress levels are associated with hypomotility (although not always replicated)
- Gut-directed hypnosis has a stronger gastroprokinetic effect than cisapride in patients with functional dyspepsia and healthy controls
- State anxiety correlates negatively with gastric sensitivity thresholds
- Sexual abuse history is associated with hypersensitivity
  Physical abuse history is associated with hyposensitivity
- Taken together, these studies epidemiological studies clearly illustrate the relevance of psychosocial factors and psychiatric comorbidity in functional dyspepsia
PATHOPHYSIOLOGY

- Knowledge of neurobiological basis of psycho(patho)logical processes
- Insight in communication between the brain and the gut: the brain-gut axis

Brain-gut signaling in health and disease

- The brain-gut axis represents an important part of an integrated interoceptive system that is continuously signalling homeostatic information about the physiological condition of the whole body to the brain
- In the brain: integration of information (homeostatic-interoceptive info, exteroceptive signals, brain-reward system, affective and cognitive brain circuits)
- This system links homeostatic signals to emotions and motivates the organism to take action to increase chances of survival
- Model of functional dyspepsia as a disorder of brain-gut signalling: see figure 1
  A) Health:
  presence of food in gastrointestinal tract --> via neurohormonal pathways --> homeostatic regions in the brain. This signalling is largely unperceived. Only salient or potentially noxious stimuli require a behavioral response
  B) Functional dyspepsia:
  Normal sensory signalling from the gastrointestinal tract to the brain might be inappropriately perceived in case of defective sensory filtering, for instance in case of an overactive reward system or an impaired descending modulatory system, which might be related to psychological processes such as anxiety or impaired cognitive inhibition. This defective sensory filtering might impair food intake regulation as well as increased perception of physiological stimuli as painful

Brain imaging studies in functional dyspepsia

- Functional brain imaging studies in healthy volunteers have elucidated (verduidelijk) the neural mechanisms underlying emotional and attentional modulation of visceral pain
- Neuroticism scores have been shown to correlate positively with brain activity (in affective and cognitive pain modulatory regions) during anticipation of pain
- Negative correlation between neuroticism and brain activity during the experience of pain
The Leuven group (using PET):
- patients with dyspepsia: activation of homeostatic-interoceptive brain regions at lower intragastric pressures than healthy controls
- during painful gastric distension, patients failed to activate the pACC (a key region in the descending modulatory system)
- during painful gastric distension, increased anxiety levels correlate with increased locus coeruleus activity
- during anticipation of gastric distension: patients fail to deactivate the amygdala

Van Oudenhove et al: used advanced techniques to demonstrate that impaired effective connectivity of the descending modulatory system underlies gastric hypersensitivity

Taken together, these results are consistent with the model (figure 1b): anxiety-related impairment of the descending modulatory system causes defective sensory filtering --> physiological levels of gastric distension are perceived as painful

Patients with abuse history:
- during gastric distension: a lack of activation of pain modulatory regions
- during gastric pain: no amygdala deactivation
--> impaired reappraisal of stimuli

Abused patients with functional dyspepsia: lack of excitatory connectivity to the pACC and lack of inhibitory connectivity to the amygdala

F-fluorodeoxyglucose-PET: assess resting brain activity in patients:
- increased activity in homeostatic-interoceptive regions
- patients with comorbid anxiety and depression:
  increased activation in the thalamus, posterior insula and somatosensory cortex
decreased activation in the midbrain cingulate cortex
- patients with acupuncture treatment:
  positive effects on dyspepsia symptoms and decreased brain activity in a number of regions
 --> improvement in symptoms correlated with decreased activity in some regions

These findings indicate that patients are also characterized by abnormal brain activity at rest (not only when in pain)

Partly correlated with anxiety and depression
These findings are consistent with the model (see fig 1): psychological morbidity leads to failure of the sensory filtering process, which in turn leads to increased processing of physiological sensory signals in homeostatic-interoceptive regions, causing these signals to be consciously perceived as epigastric symptoms.

The autonomic nervous system

- Two key brain-gut interfaces: the autonomic system and the stress hormone system
- Lots of studies with conflicting results
- Camillera et al: gastric motility and autonomic responses to stress:
  - 2 subgroups of patients:
    - hypomotility at baseline
    - normal motility at baseline
  --> groups did not differ in terms of personality, autonomic or humoral responses
- Mearin et al: no differences between patients or healthy controls in autonomic or gastric response to cold stress
- The Bergen group:
  - patients show reduced vagal tone
  - patients lack stress-induced reduction of antral motility
  - neuroticism and depression are associated with low vagal tone
  - increased sympathetic tone in patients
  - breathing exercises improve drinking capacity
  - vagal stimulation improves gastric motility
- Mush et al: subgroups on the basis of baseline autonomic activity and stress-induced autonomic variability
  - group 1: greater basal sympathetic dominance and greater autonomic variability during stress. Higher neuroticism scores.
  - group 2: less basal sympathetic dominance and less autonomic variability during stress
  --> groups did not differ in terms of symptoms
- Study from Brazil: reduced vagal tone in patients
- Korean group: contradictory findings: increased parasympathetic and orthosympathetic function in patients

Summary:
Evidence for autonomic dysfunction in functional dyspepsia is growing, although
there are conflicting results about the exact nature of this dysfunction. Moreover, Autonomic dysfunction might be the link between physiological morbidity and gastric sensorimotor dysfunction

The stress hormone system

- Johnsson et al:
  - baseline: lower prolactin levels in patients
  - in response to stress: prolactin levels rise, both in patients and healthy controls
- Trier group:
  - baseline: lower cortisol levels
  - in response to CRH: blunted (afgestompt) levels of adrenaline and cortisol (so less than in healthy controls)

Low awakening cortisol levels --&gt; high levels of pain perception
High awakening cortisol levels --&gt; depressed mood

- But: none of these studies controlled for abuse history (major determinant of HPA-function)

CONCLUSIONS

- Evidence from epidemiological studies: association between psychological morbidity (especially anxiety and depression) and functional dyspepsia
- Psychosocial factors do not merely exert an influence on health-care-seeking behavior. They have a more intrinsic role in the initiation of functional dyspepsia
- Understanding functional dyspepsia? Biopsychosocial approach!
- Pathophysiological studies have increased our insight into the mechanisms by which psychosocial factors might exert their role in functional dyspepsia
  - understanding the integration of brain-gut signals (processed in homeostatic-interoceptive brain regions, with input from the exteroceptive system, reward system and affective and cognitive circuits in the brain), helps clarify the important role of psychological factors, as well as the high comorbidity with anxiety and depression
KEY POINTS

- Epidemiological studies demonstrate a higher prevalence of anxiety and depression in patients with functional dyspepsia than in healthy individuals, suggesting an intrinsic role for these psychiatric disorders in the initiation of functional dyspepsia.
- Epidemiological evidence also suggests a role for personality traits, stressful life events in general (sexual and physical abuse in particular) and other psychosocial factors in functional dyspepsia.
- Pathophysiological studies show that psychosocial factors and psychiatric disorders might exert their role in functional dyspepsia by modulating the processing of visceral signals in the brain and through descending pathways.
- The autonomic nervous system and stress hormone system are important brain-gut interfaces through which psychosocial factors and psychiatric comorbidity might influence gastric motor function, including accommodation and emptying.
- A biopsychosocial approach to the diagnosis and management of functional dyspepsia is warranted and empirically supported by an integrated model of functional dyspepsia as a disorder of brain-gut signalling.
Class 10: Positive psychology

SLIDES
Text: Positive affect and health

Abstract

- Positive emotion/affect = feelings that reflect a level of pleasurable engagement with the environment, such as happiness, joy, excitement, enthusiasm, and contentment.

REVIEW

- The strongest links between positive emotions and health are found in studies that examine trait affective style
- Trait affective style: a person’s typical emotional experience
  State affective style: momentary responses to events

Mortality

- Study: diaries of nuns:
  the greater the number of positive emotion words and sentences, the greater was the probability of being alive 60 years later
- But: positive emotions are not generally associated with increased longevity in studies of other populations (e.g. youth instead of elderly)

Illness onset

- Persons with high levels of PA (positive affect) are less likely to develop a cold when exposed to a virus
- Trait PA has been associated with
  - lower rates of stroke among noninstitutionalized elderly
  - lower rates of rehospitalization for coronary problems
  - fewer injuries
  - improved pregnancy outcomes among women undergoing assisted fertilization
Survival

- Individuals with diseases with good prognoses (decent prospects for long-term survival), may benefit from PA.
  But: high levels of PA may be harmful to the health of individuals who have advanced diseases with poor and short-term prognoses.

Symptoms and pain

- There is evidence linking PA to reports of fewer symptoms, less pain and better health
- When objective signs of illness were held constant, those higher in trait PA reported less severe symptoms, and those higher in trait NA reported more severe ones

LIMITATIONS OF THE EXISTING LITERATURE

HOW COULD PA IMPROVE HEALTH?

- Higher trait PA has been associated with better health practices such as
  - improved sleep quality
  - more exercise
  - more intake of dietary zinc
  as well as with lower levels of the stress hormones (epinephrine, norepinephrine and cortisol)
- PA in the laboratory has been shown to alter various aspects of immune function (direction?)
- PA may also influence health by altering social interactions
- PA may also influence health indirectly. PA may influence health primarily through its ability to improve the potentially pathogenic influences of stressful life events

WHERE DO WE GO FROM HERE?
The value of positive emotions

- Nuns who expressed the most positive emotions lived up to 10 years longer than those who expressed the fewest.

Why so negative?

- Positive emotions are harder to study because they are relatively undifferentiated.
- Various physical components of emotional expression similarly reveal a lack of differentiation:
  - Facial expressions have no unique signal value (all share the duchenne-smile).
  - Positive emotions have no distinguishable autonomic responses.
- Positive emotions aren’t easily explained: from evolutionary perspective, how are positive emotions adaptive?

The broaden and build theory

- Positive emotions solve problems concerning personal growth and development.
  How?
  Positive emotions broaden person’s mindset --> build enduring personal resources.
- Experiment: picture viewing to induce emotion and assessment of ability to think broadly (global visual processing tasks).
  Results: people who experience positive emotion tend to choose the global configuration, suggesting a broadened pattern of thinking.
- People experiencing positive emotion think differently:
  - They score higher on a creativity test.
  - Clinical reasoning of physicians better: faster integration of information.
  - Negotiators were more likely to discover integrative solutions.
- Overall: when people feel good, their thinking becomes more creative, integrative, flexible and open to information.
- Even though positive emotions and the broadened mindsets they create are themselves short-lived, they can have deep and enduring effects (health, social ties, resources, ...)
- 9/11 experiment:
  Feeling grateful broadened positive learning, which in turn built optimism, just as the broaden-and-build theory suggests.
- Experiment inducing positive emotion:
  Those with positive induced emotions showed increases in psychological resilience.
Thus: feeling good does far more than “the absence of threats”: it can transform people for the better, making them more optimistic, resilient and socially connected

This insight might solve the evolutionary mystery: by experiencing positive emotions, our ancestors would have naturally accrued more personal resources and when later faced with threats, these greater resources translated into greater odds of survival.

The undoing hypothesis

- Positive emotions “undo” the lingering effects of negative emotions
- Examined by first inducing negative emotions, then positive emotion, no emotion or sadness.
  Results (physiological): feeling positive emotions leads to the quickest recovery to baseline
- At this point the cognitive and physiological mechanisms of the undoing effect are unknown
- These undoing effects may partly explain the longevity of people who experience positive emotions more often

Ending on a positive note

- How do the positive emotions promote longevity?
  - the undoing effects suggests that positive emotions reduce the physiological ‘damage’ on the cardiovascular system sustained by negative emotions
  - There is a mutually reinforcing effect between positive affect and broadened thinking --> positive emotions increase likelihood that one will feel good in the future
- Positive emotions don’t just transform individuals, but also communities and organizations
- All of this suggests that we need to develop methods to experience more positive emotions and more often. Important: finding positive meaning in current circumstances
Class 11: Genes
SLIDES
No text