Biology of burnout per biologic system (nervous, immune, endocrine) and derived set of biomarkers for somatic measurement of chronic stress and burnout

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Abstract*. In this review article, we strive towards a complete as possible description of the biology/physiology of burnout. We hereby bear in mind the sequence of stress –> chronic stress → burnout/chronic fatigue syndrome (cfs).*

We strive to be systematic through the distinction of effects of burnout in

- *endocrine system (hormones that regulates homeostases over time), and within the endocrine system: review of effects per gland*
- *immune system (for defense to external pathogens, but also to psychic cues as stressors)*
- *neural system (which is the fastest system).*

It takes hard study to be proficient in all three areas, but equal knowledge of the three is necessary be cause there are many interactions: neurons can (through neurotransmittors) act upon other neurons, but hormones can also act upon neurons, through their receptors, and hormones cannot only be secreted by glands but also by immune cells. Finally, immune cells also have receptors so hormones, as well as neurons as well as other immune cells can affect immune cells. The body usually reacts 'failsafe', i.e. more than one loop is used to generate an effect. On should always think of the three systems

About the stress endocrinology of the HPA-axis and pituatory gland ('hypofyse') a lot has been written. We would say 'amost too much about cortisol', because cortisol is not conclusive, and cortisol levels are very dependent of the time during the day.

In this article a broader perspective is taken: endocrinology, immune system and neural system are reviewed for the effects of chronic stress and burnout, and physiological measures of the burnout state are highlighted so clients are able to support a psychological diagnosis of burnout with somatic evidence.

We discern five parts:
Part A: differences and similarities of chronic stress, burnout and cfs
Part B. Endocrinology of burnout
Part C: Immune system and burnout
Part D: Neural correlates of burnout
Part E measurements

Part A: differences and similarities of chronic stress, burnout and cfs

Stress, chronic stress, burnout and chronic fatigue are different things. We shortly highlight the differences and similarities.

The word 'strtess' was only used to describe a human state since World War 2, the machine-like activities and experiences soldiers had to go through. We refer to works of Kugelmann (1992) and Selye (1950).

Sress biologically makes sense in short during danger situations, like when a predator threatens human. The subsequent stress, flight-or-fight reaction and all physiological seem to soundly promote the survival of human (Kugelmann 1992)..

However, chronic stress (often defined as 3 or more hours per day for a prolonged period) is seen as detrimental. Mechanisation, transparency through ICT and globalisation have created a society in which and increasing number of people suffers from chronic stress. In a Godly way, human was clearly made for stress but but not chronic stress, and in evolutionary sense human has clearly not yet well adapted to chronic stress.

Burnout is defined is a state of 1) emotional exhaustion 2) depersonalisation 3) low esteem of own competences (Maslach 1986, Freudenberger, 1974). In the process of chronic stress, a significant part of people 'suddenly fall ill' – which is typical of burnout: a sudden drop in (cognitive) performance, a sudden increase of emotionability. Another part of humankind endures stress until sudden death comes, without burnout (Japanese death by overwork), and others seem not to be subject to a sudden 'falling ill to burnout', but are subject to slowly decreasing cognitive peformance (van Dam 2012, 2013, van der Linden 2013), often ending in chronic fatigue syndrom, cfs.

In our practice (Stichting Burnout, 2006-2014) was saw appr. 500 clients for burnout, and as striking difference between burnout and chronic fatigue syndrom we find:

- the easy attribution of burnout to stressors and lack of energy replenishers, as seen in the BBTI (Blankert Burnout Trigger Inventory, 2014)
- the thereby effective recovery therapy of burnout
- with burnout sometimes acute and chronic pain occur, but no chronic pain at specific, constant areas as in cfs. In burnout, emotional exhaustion, emotional stress and impaired cognitive performance are obstacle to resume work, not: pains.

In the 12PS burnout recovery program (Stichting Burnout, http://burnout.nl), the quick attribution of stress to factors generates quick insights, emotional processing; external siutations as well as coping can be improved. With cfs, allocation of former stressors has become vague/impossible, so the 'analysis of pathogenesis' is of limited use for recovery of cfs.

Once people leave work with untreated burnout, the burnout transform to 1) chronic fatigue syndrom. The external stressors and energy disbalances of work have disappeared (being unemployed, for example) – but the state of 1) emotional exhaustion 2) depersonalisation 3)

lower esteem of own competences and 4) cognitive impairment has remained.

A special somatic side of cfs is that is mostly comes with chronic pain. Cfs thus involves a lot of the neural system: at least pain-reporting nocireceptors, and as we will see later also neuroinflammation in the brain (Nakatomi, 2014).

In the search for physiogical description and biomarkers of burnout, we therefore bear in mind the sequence of stress –> chronic stress → burnout (->) cfs.

That burnout is totally different from depression is obvious from psychological and certainly biological differences between both states (see Blankert 2014, differential analysis and table between burnout and depression).

Part B. Endocrinology of burnout

1. Glands involved in chronic stress and burnout

1.1. Pituatory gland ('hypofyse') and HPA axis

The hypoyhalamus (H) is the main glad of the body. Relevant to stress, it is important to know that the pituitary gland (P) secretes hormones that are INHIBITED when stress is perceived:

- oxytocin (posterior pituitary), the 'bonding' and 'growth hormone'
- growth hormhone GHRH

What is INCREASINGLY secreted upon stress consists of:

- CRH from posterior pituitary to anterior pitauitary POMC → ACTH
- effect 1: ACTH acts on adrenal cortex and secretes glucocorticoids, mainly cortisol – a steroid hormone
- effect 2: negative feedbackloop: ACTH → acts on G protein coupled receptos → inhibits ACTh release (!). This effect 2, is slower than effect 1, and attempts to regulate the overall body to a homeostatis of 'rest'. This negative feedback of ACTH on its own production happens through:
  - inhibition of CRH transcription at hypotghalamus
  - inhibition of POMC transcription at anterior pituitary gland

  (negative feedback loop of the pituitary gland)
- effect 3: Epinephrine and norepinephrine are produced by the adrenal medulla through sympathetic stimulation and the local effects of cortisol (upregulation enzymes to make E/NE). E/NE will positively feedback to the pituitary and increase the breakdown of POMCs into ACTH and β-endorphins.
  (negative feedbackloop of adrenal gland)

Effect 1, the production of cortisol: Cortisol inhibits insulin production in an attempt to prevent glucose from being stored, favoring its immediate use. Under stressful conditions, cortisol provides the body with glucose by tapping into protein stores via gluconeogenesis in the liver. This energy can help an individual fight or flee a stressor. Cortisol narrows the arteries while the epinephrine increases heart rate, both of which force blood to pump harder and faster.

Above meachanism is geniously designed for fligh-fight situations: after the initial effect of hypervigilance in order to deal with the attack, the hypervigilance is automatically regulated back to a homeostasis of rest. Also, during activation and increased cortisol, the activity of the immune system is enhanced.

Apart from the negative feedback loop, cortisol is being broken down to cortisone (which does not have the damaging effects of longlasting elevated cortisol level) by the enzym 11-beta HSD2 into cortiSONE (cortisol is made through the enzume HSD1).

Here you find the corticosteroid conversion table: cortisol is broken down to steroids with an increasing half time (cortisone half time 8-12 hours) by enzymes.

Compound	Anti-inflammatory Potency	Na^+-retaining Potency	Duration ($T_{½}$, Hours)	Equivalent Dose (mg)
Cortisol	1	1	8-12	20
Cortisone	0.8	0.8	8-12	25
Fludrocortisone	10	12.5	8-12	N/A
Prednisone	4	0.8	12-36	5
Prednisolone	4	0.8	12-36	5
6a-Methylprednisolone	5	0.5	12-36	4
Triamcinolone	5	0	12-36	4
Betamethasone	25	0	36-72	0.75
Dexamethasone	25	0	36-72	0.75

Longlasting elevated cortisol(-related) levels are adversary to a whole range of bodily processes.

In other words: upon an 'attack' the sympathetic system is activated, but once the attack is dealt with (usually in less than half an hour), the body system automatically switches back to activate the parasympathetic system after wich rest is regained. The interesting point about the sympathetic and parasympathetic system is that only ONE of them can be active at any point in time. The switchting forth and back, from sympathetic to parasympathetic is crucial to switch between appropriate hypervigilance and rest (Hampson, R., 2007).

Our thesis is that the human body is perfectly designed to cope with stress, but very unfit to deal with chronic stress (which is defined as 3 hours of more of stress per day, over a prolonged period of time). We will re-encounter this hypothesis several times in this article.

This thesis is supported by the fact that never before the Industrial Revolution mankind wrote about stress. An early effect of Industrial Revolution has also been converged into film by Charlie Chaplin in 'Modern Times' (1936). The most notorious stress philospher Robert Kugelmann holds the hypothesis that stress in fact did not exist before Second World War (Kugelmann, 1992). In many descriptions of First World War, it can be read that soldier of opponing trenches held pauses, to eat stretch and walk around, with the agreement that no party would shoot. Upon a sign, both opponents would retreat in their trenches and continue to shoot. Even in a world war, industrialisation was not far enough as to produce constant stress, chronic stress.

1.2 Dysfunctional HPA axis

The HPA axis become dysfunctional, when the 'switch back to resting state' is deregulated.

The HPA-axis can become either

A) hyperregulated (after which the human (or rodent, in experiments) constantly remains in a hypervigilant state; cortisol is constantly secreted but only slowly broken down, and the negative feedbackloops of ACTH inhibiting its own release, and E/NE inhibiting ACTH release are not enough to return to rest (Houdenhove 2006)
B) hyporegulated. The mechanism of hyporegulation can be multiple, as described by and Kudielka et al 2006, 2013, Newman 2013 and Cara Thomas 2013 for cfs.

Hyporegulation and hypofunctioning of the HPA axis are the case in amongst others chronic fatigue syndrom (cfs) and burnout. In its strive to remain healthy, the body has to make the controversal choice between a hyperactive HPA axis with all long term damage of elevated cortisol levels, or a hypo active HPA axis having the disadvantage of chronic exhaustion, vital exhaustion, chronic fatigue, burnout.

From a therapeutic point of view it is very important to prevent a dysfunctioning of the HPA-axis, and once it is dysregulated, to get it balanced again. Emotional awareness, Affection Regulation Therapy, learning to switch soundly again between sympathetic and parasympathetic system, awareness of hormonal changes in the body may all add.

1.3 Endocrine measurement of dysfunctional HPA axis

Scientific literature anno 2014 is in agreement that chronic stress can lead to quite different metabolic processes underlying a hyperactive or hypoactive HPA-axis, so no conslusive measurement is possible yet.

Mommersteeg 2006 investigated hormonal changes under stress and chronic stress and found cortisol measurement unconclusive.

Fortunately in recent years (2006+) some clear progress was made regarding measurement of the HPA-axis, and fortunately most researchers are aware that dysfunction of the HPA-axis can result in hyperactivity, hyporeactivity or irregular activity.

In 2011 Elizabeth I. Flandreau et al. Conducted a research in which

- elevated CRF Corticotropin-releasing factor (CRF) was found in cerebrospinal fluid, due to overproduction by the central amygdaga (CeA). The amygdala is known as long term emotional memory, and also fear center. In chronically stressed people, the amygdala is usually overactive (and the hippocampus shranked, bu 10-20%)
- the overactivity of amygdala was confirmed by fMRI neuroimaging

Measurement: the Dex/CRF combination test is considered by many to be the most sensitive measure of HPA axis activity. , reflecting both fee-back and feed-forward mechanisms (Heuser et al., 1994, Gutman 2003, Ising et al 2005, Flandreau et al. 2011).

In the CRF simulation test, a blunted Acth response is found, as well as non-suppression of DST.

DST non-suppression goes along with insufficient negative feedback. A blunted CRF response is attributed to decreased CRF1 expression in the anterior pituaitary secondary to the chronic hypersecretion of CRF from the hypothalamus and/or negative feedback of cortisol on the corticotroph (Flandreau et al 2011)

If in the Dex part of the Dex/CRF test elevated ACTH and cortisol concentrarions are found, this suggests that gluco-corticoid (GC) and CRF overexpression contribute to HPA axis hyperactivity.

The DST (dexamethasone suppression test) proved to be too unsensitive to make valid conclusions (Pruessner et al. 1999; Sonnenschein et al. 2007; Bellingrath et al. 2008; Mommersteeg 2006).

An improvement of the DST is the DEX-CRH test (dexamethasone-corticotropin releasing hormone test). Here, the HPA axis is re-tested after prior administerd suppression. The paradgim is desigend to test joint pituitary and adrenal cortex reactivity.

The DEX-CRH test should preferably be followed by a low dose ACTH1-24 Synachten test. In contrast to the DEX-CRH test, the Synacthen test is used to trigger immediate cortisol secretion from the adrenal cortex. Therefore with application of the low dose synthetic ACTH, the response sensitivity of the adrenal cortex can be tested pharmacologically (Flandreau et al. 2011). And: the presumption of a 'adrenal fatigue' can be tested pharmacologically.

2 Thyroid gland ('schildklier):

Two of the most important hormones are secreted by the thyroid gland are T3 and T4, triiodothyronine (**T3**) and its prohormone, thyroxine (**T4**),. They are crucial for the body's overall metabolism. 93% of the hormone produced by the thyroid gland is T4 and it is inactive.

Before it can be used by cells, it must be converted to T3. Adrenal stress and inflammatory cytokines reduce the conversion from T4 to T3 and thus reduce overall metabolism.

The conversion from T4 to T3 is catalyzed by enzyme 5′-deiodinase in peripheral tissues such as the liver and the gut.

Enzymes that suppress the conversion of T4 to T3 are: Th1, Th2 inflammatory cytokines , IL-6, TNF-alpha, IFN-gamma and IL-1 beta. IL6 is a marker of inflammation. As inflammation increases, levels of active serum T3 fall.

In order for thyroid hormone T3 circulating in blood to have a physiological effect, it must first activate receptors on cells. Inflammatory cytokines have been shown to suppress thyroid receptor site sensitivity. It is not possible to measure T3 in a clinical setting.

Prolonged cortisol elevations, caused by chronic stress, decrease the liver’s ability to clear excess estrogens from the blood. Excess estrogen increases levels of thyroid binding globulin (TBG), the proteins that thyroid hormone is attached to as it’s transported through the body.

When thyroid hormone is bound to TBG, it is inactive. It must be cleaved from TBG to become “free-fraction” before it can activate cellular receptors. (These free-fraction thyroid hormones are represented on lab tests as “free T4 [FT4]” and “free T3 [FT3]”.)

When TBG levels are high, the percentage of free thyroid hormones drops. This shows up on labs as low T3 uptake and low free T4/T3.

A high T4 to T3 ratio, to be measurend by Elisa, would thus be a good measure for chronic stress – though other factors may influence the T4 T3 ratio as well.

3 Adrenal gland ('bijnier'):

The adrenal medulla is part of the ANS (anatomous nerve system) and sympathetic system, and secretes adrenaline (epineprhine) as well as noradrenaline (norepinephrine).

The adrenal gland secretes:

- glucocorticoids, produced in response to stress
- mineralcorticoids, regulating blood volume
- androgens, controlling sexual devcelopment

Cortisol has effect an the adrenal gland and can

- increase proteint metabolism (breakdown of proteints, cells in general)
- increase fat metabolism
- suppress the immune system by suppressing production of cytokines, antibodies (and thereby suppress inflammation)
- suppress endocrine system incl. ACTH, LH, FSH, TSH and GH (growth hormone)
- increase working of sympathetic system

The adrenal gland is part of effect 4 in paragraph 1.2: negative feedback loop to the HPA-axis in case of stress – helping restoring homeostasis.

The assumption of 'adrenal fatigue' is that the adrenal gland is 'tired' of providing this constant feedback to the pituitary gland. Adrenal fatigue is however very difficult to measure, as it – until now – boils down to cortisol measurement, which is not conclusive at all as mentioned in par. 1.3

4 Pineal gland (pijnappelklier):

The pineal gland receives innervation from the:

- SCN, Suprachiasmatic nucleus
- retina (sight)
- sympathetic system
- parasympathetic system

The pineal gland produces amongst others melatonine, which is a very important sleep hormone.

Thus stress, influencing sympathetic and parasympathetic quickly influences melatonin and sleep (the non-Zeitgeber circadian rhytm comes from SCN, ' free running').

In very disstressed people, melatonin levels can be very low which makes 'falling asleep' difficult. The falling asleep is then not anyomore induced by a hormone, but is purely dependent of keeping

neurons hyperpolarized, by release of GABA in the VLPO or by benzodiazepines. Sleeps then sets in 'without warning' from sleep hormones. See chapter 5 for the neural mechanism of falling asleep.

TH, tyrosine hydroxylase , is made by the thyroid gland but is present in the pineal gland – it is a biomarker of the sympathetic system. **Tyrosine hydroxylase** or **tyrosine 3-monooxygenase** is the enzyme responsible for catalyzing the conversion of the amino acid L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) does so using molecular oxygen (O2), as well as iron (Fe2+) andtetrahydrobiopterin as cofactors. L-DOPA is a precursor for dopamine, which, in turn, is a precursor for the important neurotransmittersnorepinephrine (noradrenaline) and epinephrine (adrenaline)

Dagnino-Subiabre et al. (2006) found that chronic stress significantly reduces the sympathetic marker TH in the pineal gland.

Thus, chronic stress reduces metabolism, amongst others through the just mentioned mechanism: chronic stress reduces TH in the pineal gland. This is another negative feedback loop to stress.

TH (measurement) is thus a good biomarker of chronic stress. The **enzyme-linked immunosorbent assay** (**ELISA**) , can be used for the measurement of TH.

Part C: Immune system and burnout

1. Immune system: weakened by chronic stress

Immune cells surveille the whole body. Most can go in and out of blood vessels, some can even pass cell membranes or otherwise move through non-enclosed fluid. Immune cells surveille til the skin, and react immediately to stress.

The GI (**human gastrointestinal tract**, or **GI tract)**, is an organ system responsible for consuming and digesting foodstuffs, absorbing nutrients, and expelling waste. The GI tract, lungs and the blood-brain barrier are the primary immune barriers in the body. They prevent foreign substances from entering the bloodstream and the brain. Adrenal stress weakens these barriers, weakens the immune system in general, and promotes poor immune system regulation.

When these immune barriers are breached large proteins and other antigens are able to pass into the bloodstream or brain where they don't belong. If this happens repeatedly, the immune system gets thrown out of whack and we become more prone to autoimmune diseases such as Hashimoto's.)

Interleukins are a group of cytokines (secreted proteins and signaling molecules) that were first seen to be expressed by white blood cells (leukocytes).[1] The function of the immune system depends in a large part on interleukins

2. Significant lower IL-10 levels when chronic stress

Interleukin-10 (**IL-10**), also known as **human cytokine synthesis inhibitory factor** (**CSIF**), is an anti-inflammatory cytokine. In humans, IL-10 is encoded by the *IL10* gene

Mommersteeg 2006 proved chronic stress to go along with clearly lower IL-10 levels.

Brenu et al. 2011 proved cfs/ME to go along with clearly lower IL-10 levels.

The research was published in the May 2011 issue of the Journal of Translational Medicine. The paper, "Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis", was authored by a team of scientists at Bond University in Australia and by Dr. Nancy Klimas, a respected and long-time CFIDS researcher in Florida.

The study is one of the most recent, major research papers investigating detailed immunological abnormalities and functioning in CFS/CFIDS/ME. The study builds on two decades of past research into impaired immune function in the illness, but also presents some new findings regarding certain immune processes.

Moreover, the 52 citations of major research papers present an important review of research bearing on immunological abnormalities in CFS/CFIDS/ME.

The study included 95 Australian subjects who met the 1994 CDC criteria for CFS and 50 qualified healthy controls. It found that CFS/ME patients had significantly higher levels of the anti-inflammatory cytokine interleukin-10 (IL-10) and two pro-inflammatory cytokines gamma

interferon (IFN-γ) and tumor necrosis factor alpha (TNF-α), as well as increases in CD4+CD25+ T-cells and expression of FoxP3 by T regulatory cells and VPACR2

Thus: IL-10 is another biomarker of chronic stress/burnout; this weakening (IL-10 decrease) of the immune system prolong the inflammations (as IL-10 is anti-inflammatory).

3 Significant higer levels of pro-inflammatory IL-6 with chronic stress and age

Kiecolt-Glaser - 2003 and there after many others identified IL-6 biomarker of (neuro)inflammation. Together with the other biomarkers mentioned in this article, an increased IL-6 level may be taken as strong evidence of chronic stress (but: correct for age).

Taken together, chronic stress significantly raises the level of pro-inflammatory IL-6 and significantly lower the level of anti-inflammatory IL-10.

This makes it plausible that chronic stress works pro-inflammatory, as well as through higher IL-6 as lower IL-10.

Part D: Neural correlates of burnout

As usual in this review, we start with stress and chronic stress.

1 Sympathetic and parasympathetic system

1.1 Introduction Sympathetic and parasympathetic system

Upon a stressor from outside, as well the CNS (Central Nervous System) and ANS (Autonomic Nervous System) are activitated.

Biologically, the ANS reaction to stress makes a lot of sense because stressor reaction through the cognitive system may take too long – local 'intelligent' reactions through the ANS are required. Furthermore, it is good to bear in mind that the conductance speed of neurons, best in pyramid neurons maximally mylyenated, worst in ad hoc networks of ummylenated neurons, is 0,5 to 15 meter per second. The travel for a signal from toe to top and back may bee to late for a reaction to a stressor, and is certainly too late for top scorers in football. Latter, scoring in football, is not a life necessity, but illustrates the 'intelligence' the ANS can have.

The **peripheral nervous system** (**PNS**) is the part of the nervous system that consists of the nerves and ganglia outside of the brainand spinal cord. The main function of the PNS is to connect the central nervous system (CNS) to the limbs and organs, essentially serving as a communication relay going back and forth between the brain and the extremities.

The **autonomic nervous system** (ANS), also known as the **visceral nervous system** and **involuntary nervous system** — is a division of the peripheral nervous system that influences the function of internal organs. The autonomic nervous system is a control system that acts largely unconsciously and regulates the heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. This system is the primary mechanism in control of the fight-or-flight response and its role is mediated by two different components.

The sympathic nervous system stems from the cranial automatic outflow and the parasympathetic from the spinal automatic outflow.

Autonomic functions include control of respiration,cardiac regulation (the cardiac control center), vasomotor activity (the vasomotor center), and certain reflex actions such as coughing,sneezing, swallowing and vomiting. Those are then subdivided into other areas and are also linked to ANS subsystems and nervous systems external to the brain. The hypothalamus, just above the brain stem, acts as an integrator for autonomic functions, receiving ANSregulatory input from the limbic system to do so.

The autonomic nervous system has two branches: the sympathetic nervous system and the parasympathetic nervous system. The sympathetic nervous system is often considered the "fight or flight" system, while the parasympathetic nervous system is often considered the "rest and digest" or "feed and breed" system. In many cases, both of these systems have "opposite" actions where one system activates a physiological response and the other inhibits it. An older simplification of the sympathetic and parasympathetic nervous systems as "excitory" and "inhibitory" was overturned due to the many exceptions found. A more modern characterization is that the sympathetic nervous system is a "quick response mobilizing system" and the parasympathetic is a "more slowly activated dampeningsystem", but even this has exceptions, such

as in sexual arousal and orgasm, wherein both play a role.

In general, the autonomic nervous system functions can be divided into sensory (afferent) and motor (efferent) subsystems. Within both, there
are inhibitory and excitatory synapses between neurons. Relatively recently, a third subsystem of neurons that have been named 'non-adrenergic and non-cholinergic' neurons (because they use nitric oxide as a neurotransmitter) have been described and found to be integral in autonomic function, in particular in the gut and the lungs.

Although the ANS is also known as the visceral nervous system the ANS is only connected with the motor side. Most autonomous functions are involuntary but they can often work in conjunction with the somatic nervous system which provides voluntary control.

1.2. Stressor is recognised by the voluntary / central nervous system

A stressor can be recognised by one of the five human senses; signals are neurally transported to the sensory cortex. Right next to the sensory cortex is the motor cortex, is immediate motory action can be undertaken to 'fight of flight' a stressor

1.3 Stressor and the unvoluntary / autonomic nervous system

Because a) what has to be regulated upon stress is TOO MUCH to be regulated centrally b) central response may be too slow, an 'unvoluntary' or 'autonomic nervous system' exists. A sudden stressor leads to vasoconstriction results from the increased concentration of calcium (Ca^{2+} ions) within vascular smooth muscle cells. The result is that muscles are ready to act.

All in the body, including internal organs an a large variety of parameters that would be too much to be regulated by the CNS, are regulated by the ANS, and in case of stress it is the sympathetic nerve system that sets the whole body in a stage of 'flight of fight'.

The sympathetic descending system stems from the cranial automatic ouflow and neurons are innervated up to the ganglia. The postganglic sympathetic neurons are noradrenergic, and go to all internal organs up to the skin. There is also a flow of information back, which is the ascending flow of information.

Upon stress, the body system is OUT of its 'homeostase', something that can be regulated only by stress (into sympathetic state, or after stress: back to homeostase and parasympathetic system) or by hormones/the endocrine system.

Upon stress, the parasympathetic system is abruptly 'cut off' and the sympathetic system is 'in'. The recovery/return to homeostatis only happens slowly: the cortisol related chemicals have to be broken off (which takes many hours), and the parasympathetic system must be in control again.

The parasympathetic system starts with the cranial nerves III, VII, IX and X=vagus nerve, and go straight to the internal organs (not via ganglia). Furhter exemplary information is available on the web – Rick Hamson PhD, 2007, see also through http://burnout.nl. World's most most reknown expert in matter is prof. Wilfred Jänig, who research the ANS whole of his life, which resulted in the magnus opus 'The integrative action of the autonomic nerve system', Neurobiology of homeostasis, Cambridge University Press 2006.

1.4 Switching back and forth between sympathetic and parasympathetic nerve system; relationship to stress and chronic stress

In the largest part of existence of humankind, typically stress occurred for a short time, after which a stress response automatically gave negative feedback to its origin in order to calm down, from half an hour to hours after the initial, acute stressor.

In normal history, no chronic stress was present. Scientists agree that chronic stress is not natural, detrimental to health and that chronic stress (usually defined by: 3 or more hours of stress per day) is detrimental to health.

In a 'normal' or traditional world, the switchting forth to sympathetic mode, and switching back to parasympathetic mode is very well regulated.

In modern society (usually set at Second World War, see also Kugelmann), increasingly more chronic stress appears, which is detrimental to natural balancing from sympathetic to parasympathetic state, whis naturally regulated by:

- the endocrine system (see part B)
- the autnomous = unvoluntary nervous system (see above all: Wilfried Jährig, The integrative Action of the Autonomic Nervous System, Neurobiology of homeostatis, Wilfrid Jährig, Cambridge University Press, 2006 AND 'Relaxed and Contented; activating the parasympathetic wing of your nervous system' by Rick Hanson PhD, 2007, burnout.nl)

The de-learning of a natural switch-forward and switch-back from the sympathetic system can lead to a whole series of dysregulated homeostates (allostastases), effecting the nervous and immunological system as well, as therefore a long series of illnesses, usually to begin with: sleeping problems.

1.5 Sympathetic vs. Parasympathetic/vagus nerve activity in burnouts

The switching of sympathetic to parasympathetic system was studied amongst others by Zandstra et al. 2006, in: 'Vagal and Sympathetic Activity in Burnouts During a Mentally Demanding Workday'
Zanstra, Ydwine J.; Schellekens, Jan M. H. PhD; Schaap, Cas PhD; Kooistra, Libbe PhD

The conclusion is: ' Burnouts and healthy controls differ in their pattern of sympathetic-vagal activity only after long-lasting work demands. Findings give limited support to Porges's view that in healthy subjects, the vagal system is more responsive to challenging task situations than in chronically stressed individuals. '

Burnouts are thus 'handicapped' on long tasks, and have an 'abnormal' symp-parasymp switching. The symp-parasymp switching has to be re-learned.

But before doing that, it seems wise to analyse the situation that has led to burnout – such is possible with the BBTI (Blankert Burnout Trigger Inventory). Onze circumstances affecting stress and energy replenishment are adressed, it makes sense to relearn human symp-parasymp switching.

2, CNS: amygdala, hippocampus and PFC mechanism with chronic stress

The emotional part of the brain is the most inner part, called the 'limbic system'. Important part of this system is the 'amygdala', long term emotion memory...sometimes also called 'fear center'. Memories are retrieved from the amygdala by the hippocampus. And – the amygdala can come up with emotional memories of its own.

When the amygdala comes up with memories, emotions, it can 'project' (fire neurons, electrical signal being passed on by each neuron) towards the PFC, Pre Frontal Cortex, were we do 'active calculation'.

What often happens when there is lots of chronic stress, is, apart from earlier described effects in the endocrine system and immune system, is that the amygdala gets overactivated by fear. The amygdata then sends to the PFC, and chances are high that there 'catastrophising thoughts' are made, or at least 'anxiety related thoughts'. The PFC also projects back to the amygdala, and so a 'back and forth activiation of fear (in amygdala) and cortex' can occur. As we are not talking hormones here, there is not really a natural feedback loop of homeostases.

Human can get into a hypervigilant state, constant panic state, of close to that.

Insomnia is closely related to this hypervigilant state, and if insomnia in itself becomes ANOTHER fear, the fear system never naturally comes to rest – it can only be 'broken' by pills.

Bear in mind that with natural stress, there are feedback loops to automatically regain homeostasis = resting state. With chronic stress, there is no natural feedbackloop anymore functional in endocrinology, and there is certainly none in the nervous system.

Thus, chronic stress (3 hours or more per day stress) is an unnatural environment for which humans are not made, and no 'intelligent mutation' yet has occurred in order to bring back human to rest after a prolonged period of chronic stress. Remember the at that time very rare 'shell shock' soldiers from WO1, or post traumatic soldiers and others as from WO2 on. Lying awake for weeks with no real sleep can also become a trauma, and induce post traumatic stress disorder that will never allow normal sleep again (it can take decades of swallowing pills, re-learning the switch between sympathetic and parasympathetic state, and a zero-stress environment in order to re-learn sleep if there was once chronic insomnia in your life.

Neurons do not automatically get their rest, in the brains, and this is a danger. Francis Crick in 1995 mentioned that sleep, or unconsciousness (which are approximately the same) can be reached as soon as less than 100.000 neurons in a human are aware. The reader is referred to the excellent 2014 book 'Neuroimaging consciousness' by Springer.

When neuroimaging the brain, one should get clearly further than making anatomical images. The firing patterns of neurons are very interesting too, and the mathematical calculation and representation of firing patterns into FUNCTIONAL imaging is very useful. Functional imaging is a representation of the brain based on firing patterns, NOT anatomy. In brain research one can go one step further and deduct cause-effect series, presumably time-series, from the functional series and then be left with EFFECTIVE brain imaging (Olav Sporns, 2010).

Thanks to modern mathematics as by Watts & Strogatz 1998 ('small world representation') we can talk nowadays about an 'operating system' of the human being; this 'operating system', DMN standing for Default Mode Network, is not a network you can point out on a topographic or anatomic map, it is a mathematically functionally derived network. But it makes a lot of sense to talk about it, as we will do in paragraph 4, in relation to our theme (stress, chronic stress, burmout and chronic fatigue syndrom).

3. Nocireceptors – pain reporting in cfs

In the illnesses we consider to be sequential, or at least affiliated: stress, chronic stress, burnout and chronic fatigue syndrom (cfs), only one deals with pain: being cfs. Towards the 'falling ill' in burnout, in most cases (Stichting Burnout 2006-2014) somatisations are observed, but they are temporarily and of unpredictable place and nature.

It is only in cfs that patients report consistent daily pain, pain 'like in muscles, tissues and bones'.

This makes it very important for cfs to dig into the issue of 'pain' and how pain is 'regulated'.

Pain is regulated by 'noci-receptors'. Receptors are special proteins in the cel membrane of a cell, mostly: neuron. From outside the cell, certain molecules that have 'affinitity' with the specific kind of receptor, kan bind. This has consequnces for the influx and outflux of electricity in the neuron, and the firing or not firing of a neuron towards a next neuron. This field is called 'neurophysiology'. By passing on electrical signals, a speed of information transfer can be reached that is impossible by just 'movement of molecules'. So: real electrons, protons and electric currents are generated in the body. It was in 1780 Luigi Galvani who was the first to discover that electricity was present in animals/humans – in this case he discovered it on the frog. It took until 1956 that Nobel price winners Hodgkin and Huxley described electric neurophysiology, experimented with a giant neuron of a squid.

In the decades thereafter, many kinds of receptors were discovered, as well as neurotransmitters and other chemicals that act upon receptors.

Pain is handled by 'nocireceptors' in the body.

Neurons are sometimes 'ending free' in direction of the skin, or have a special sensory cell in order to pick up a signal from the environment (like heat, touch etc.). Most neural fibers end in a noci-receptor. The FUNCTION of a noci-receptor is to signal a CHANGE from a homeostasis. A change in temperature, tissue etc. is percepted by a nocireceptor, and this signal is 'ascending' to the brains. The signals from 'nociception' arrive in the CNS, Central Nervous System, and 'pain' is then the unpleasant emotional experience that usually accompanies nociception (the emotion of pain is generated by involvement of our limbic system = emotional system in the brains).

The electric signalling through neurons is not equal to the speed of light, but far lower. The conductance speed of neurons is in the order of 0,5 to 70 meter/second, depending on the 'isolation' of neurons, called 'myenalisation'. The higer the myenalisation, the higher the conductance speed. Afore is mentioned in order to give all readers a sign of recognition, remembering experiences with your hand accidentally on a hot stove; the pains comes only after fractions of seconds, and you are burnt – hopefully only lightly, with a pain for a couple of hours. The nociceptors immediately reported the large change of temperature to the brains, and it was then translated in emotion, being

'pain'. The reflex of retrieving your hand happens through the autonomous nervous system, fotunately, that is quicker than the case in which you would have to think out a retrieving action cognitively.

Often occurring myelinated fibres are C and A, like Adelta, Abeta, Aalfa. Nociceptors respond to noxious cold, noxious heat., a high threshold mechanical stimuli as well a variety of chemical mediators. The basic function of nociceptors is to transmit information to higher-order neurons about tissue damage.

Signals can be modulated in strength by 'modulators', other chemicals in your body. So a nociceptor signal can be 'upregulated' or 'downregulated'.

An example of this is when noxious stimuli resulting in tissue damage often lead to an increase in the response of subsequent painful stimuli, calles 'hypersensitivity', that is, an excessive sensitiviness or sensibility to pain. Hypersensitivity consists of both primary hypersensitivity, an increased sensitivity within the injured area predominantly due to peripheral nociceptor sensitisation, and secondary hypersensitivity, an increased sensitivity in the surrounding uninjured area mediated centrally.

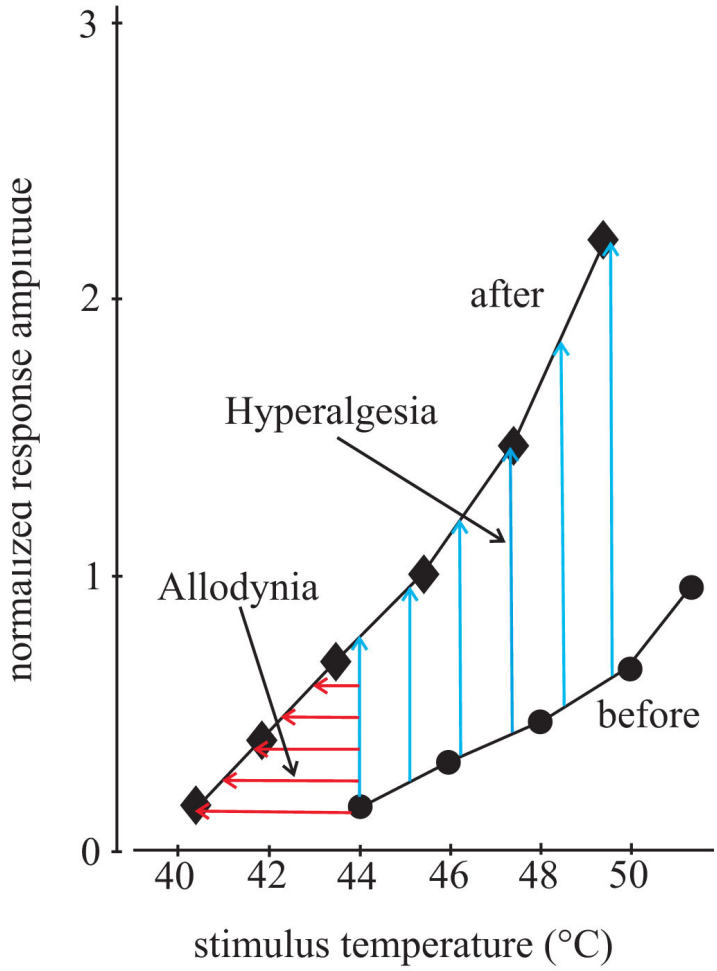


Figure: sensitisation is a leftward shift (that is toward lower intensities) of the stimulus-response curve, which relates the magnitude of the neural response to the stimulus intensity.

In chronic fatigue syndrom, cfs, hypersensitity or hyperalgesia are often the case. So in fact it is:
– hypersensitiviy of local noci ceptors
– hypersensitivity of central nervous system
– partially 'mental' as well.

The important point to make here is that cfs is not ONLY mental, physicians that would say that are not up to date regarding pain and nocireceptors.

De-sensitisation would be a good target for cfs therapy. Pharmacology found that exposure to 'Capsaicin' can result in subsequent desensitisation, through acting upon the TRPV1 nocireceptors.

The natural ligand that should be provided by nature, for pain inhibition, is 'endovanilloid'. However, cfs patients seem to have a shortage of this natural ligand (being one of the explanations). The cells needing a pain inhibitor like 'capsaicin' are very large in variety; therefore it is not possible yet to inhibit all pain with a 'blocker' as mentioned.

Apart from TPRV1, a series of other nocireceptors exist.

Modulation

Several chemicals, named 'mediators', exist that can increase or decrease the nociceptors that lead to pain. Pain scientists distinguish two aspects of sensitisation: 'allodynia' (pain resulting from a normally innocuous stimulus) and 'hyperalgesia' (an enhanced response to a normally painful stimulus).

Serotonin or 5-HT is one of these mediators; injection of it produces pain and hyperalgesia. Bradykinin produces a dose-dependent pain and heat hyperalgesia. There is a series of mediators, but their working can be quite complicated: one blocks off the other mediator, what are the pathways etc.

Neurons working in reverse direction: neurogenic inflammation

A special kind of pain is occurring when neurons are used in the reversed direction than intended. Some neurons are meant 'one way', some are meant 'bi directional', but sometimes neurons are used in the inverse way while they were not designed to function in that direction. This is called 'neurogenic inflammation'or 'erythema' (reddening of the skin), when action potentials are conducted in the direction opposite to normal.

The resulting depolarisation of terminals causes the release of the neuropeptides, substance P (SP) and calcitonin gene-related peptide (CGRP), which in turn act on target cells in the periphery such as mast cells and vascular smoot musle producing inflammation. Latter inflammation is characterised by redness, warmth and swelling (Fein, 2012).

Low pH

Injection of acidic solutions (pH 5.0-6.0) cause intense burning pain (Issberner, Reeh et al. 1996) and a substantial decrease in synovial fluid pH (6.6-7.4) is found in inflamed joints (Treuhaft and McCarty 1971).

Nerve Growth Factor (NGF)

Nerve Growth Factor (NGF) is a trophic factor that promotes the survival of nocireceptors during development. NGF is strongly involved in regulating the sensitivity to pain in adult animals (Fein, 2012).

4. cfs pain modulation; neurgenetic pain

The capacity to experience pain has a protective function:

1. it warnes us against existing or impending damage to the body and
2. evokes responses that minimize the damage.

That is, acute or nociceptive pain is a necessary protective mechanism. In contrast: CHRONIC pain serves no obvious survival or helpful function. Among the different types of chronic pain is peripheral neuropathetic pain (or peripheral neuralgia) the essential feature of which is pain resulting from a wound or damage to a primary nociceptor.

Neuropathic pain is often intense and unrelenting and resistant to relief by available therapies. Chronic pain without evidence of a lesion or damage to the primary nociceptor as in a migraine is not considered neuropathic pain. The injury may be in any part of the nociceptor and may be the result of any number of possible insults to the nociceptor. Although the insult in peripheral neuropahtetic pain is to the primary the changes underlying the neuropathic pain syndrome may include changes to the peripheral nervous system, the spinal cord and central nervous system. In this chapter we will focus on those changes thought to occur in the peripheral nervous system.

Symptoms of peripheral neuropathic pain can include persistent of paroxysmal pain, ubrning, prickling, ithcing or tingling that is independent of any obvious stimulus. There can also be abnormally heightened sensations such as allodynia (pain resulting from a normally innocuous stimulus) and hyperalgesia (an enhanced response to a normally painful stimulus). Intuitively, one might think that when an afferent nerve is injured it would fail to transmit information to the spinal cord. That is, one might reasonably expect a loss in sensations rather than a heightened or persistent sensation. 'The telephone line is cut'. To the extent that there may be some loss of sensation associated with peripheral neuropathetic pain the analogy to the telephome line holds true. However, the enhanced response and the presence of pain in the absence of a stimulus imply that there is something fundamentally different between a damaged neuronal axon and a cut telephone cable. The question then becomes what kinds of changes occur when a nerve is damaged that might give rise toi neuropathic pain?

Functionally, the spinal roots are classically divided into dorsal roots for sensory transmission and ventral roots for motor transmission. The ventral roots are thought to be composed of the axons of myenilated motor neurons. However, in humans and other mammals on the order of one third of all axons in the ventral roots are unmyenilated, have their cell bodies in the doral root ganglion, and are predominantly nociceptive. This probably explains why rhizotomy, a procedure in which the spinal cord is severed, sometimes fails to provide relief from chronic pain. Furthermore, these types of

lesions where the dorsal roots are severed have not been found to cause neuropathetic pain un humans. Therefore one can say that not all lesions to ncoiceptors result in neuropathic pain. (Fein, 2012).

Examples of neuropathic pain:

- complex regional pain syndrome type II (causalgia)
- trigeminal neuralgia

Some examples of the diversity of the treatments for neuropahtic pain:

- Gaba-pentin
- Artemin
- Cannabinoids
- HCN channels

What is the role of spontaneous activity?

It was mentioned earlier that following nerve injury nociceptors innervating the skin become sensitised to both mechanical and thermal stimuli. Thereby providing evidence that nociceptor sensitisation can contribute to the neuropathic pain state. Since allodynia and hyperalgesia can result form changes that occur centrally, it might be that spontaneous activity leads to centrally mediated hyperalgesia. It has been shown that electrical stimulation of C-fibres in humans can lead to hyperalgesia, indicating that electrical activity of C fibres in humans can lead to hyperalgesia, indicating that electrical activity in C fibres in humans can lead to hyperalgesia, indicating that electrical activity in C fibres is sufficient to produce centrally mediated hyperalgesia (Klede, Handwerker et al. 2003). Ongoing spontanous activity in the injured neuron is not necessary to produce neuropathic pain. An L5 ganglionectomy in which all the L5 afferents are removed resulted in mechanical hyperalgesia comparable to that for spinal nerve ligation (Sheth, Dorsi et al. 2002). The authors proposed that 'interaction between degenerating neurons of the injured nerve and intact affferent fibres of neighbouring nerves play a critical role for both initiation and maintenance of the mechanical hyperalgesia in neuropathic pain'.

Neuropathic, finally, can also result from demyenilation. However, little activity is than spontanous, it is more of a chronic pain.

In summary, multiple sites are altered following nerv injury. Abnormalities can occur both in injured and non-injured nociceptors innervating the affecting region. These effects include spontaneous activity, as well as allodynia and hyperalgesia. Central affects specifically sensitisation following nerve injury can also occur, though their mechanisms are not considered here.

Interposed between the initial detection of a noxious stimulus by nociceptors and the conscious appreciation of pain is a complex series of mechanisms whereby the noxious stimulus is encoded and progressively tarnsmitted to and processed by higher centers of the nervous system until it is perceived as pain. This process begins in the periphery, in the Dorsal Horn (DH) of the spinal cord.

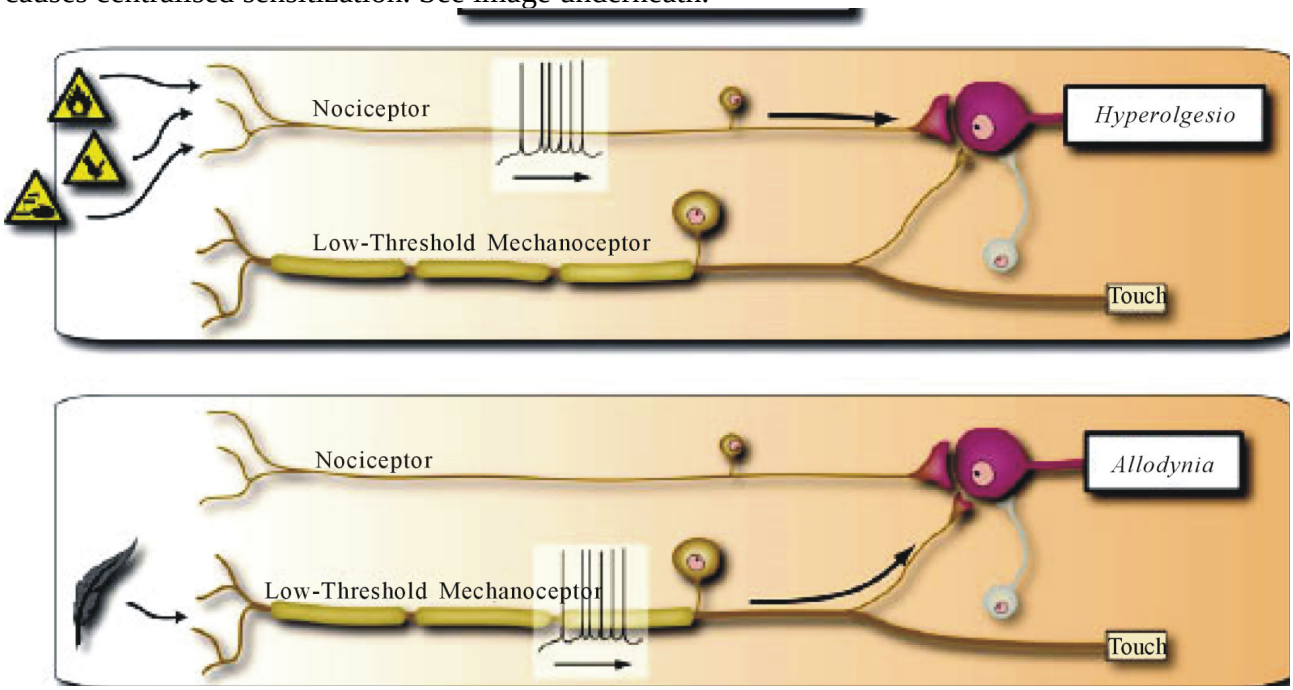
Functionally, the spinal roots are classically divided into dorsal roots for sensory transmissioan and ventral roots for motor transmission. The several roots are thought to be composed of the axon myenilated motor neurons. However, in humans and other mammals on the order of one third of all

axons in the ventral roots are unmyenilated, have their cell bodies in the dorsal root ganglion, and are predominantly nociceptive. This probably explains why dorsal rhozotomy, a procedure in which the spinal berve root between the dorsal root ganglion (DRG) and the spinal cord is severed, and sometimes fails to provide relief from chronic pain (Fein, 2012).

5. Another potential central sensitivy increasing mechanism: the switch from:noxious stimuli form low-threshold mechanoreceptor switchting over to nociceptor pain nucleus

As described by Tasagareli 2013, another mechanism occurring is the passing on of noxious (innocent) stimuli going along the myenilated mechanoreceptor 'stepping over' to the nociceptor axon leading to a (nociceptor) pain nucleus.

Thus, an insignificant mechanical stmimulus steps over to the wrong/nociceptor circuitry and causes centralised sensitization. See image underneath.



6. cfs from spinal cord to brain

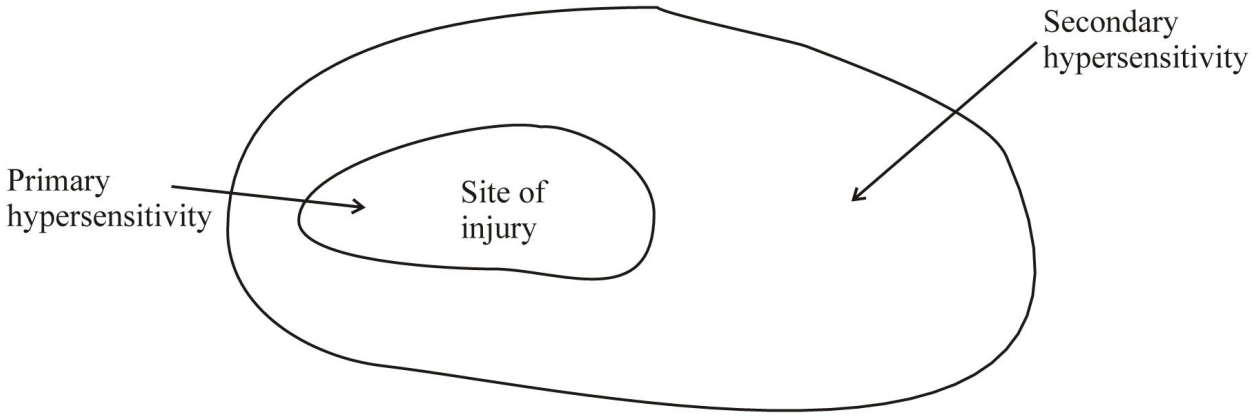
Spinal cord procesing of nociceptie signals

One can think of the spinal cord as a black box with inputs and outputs: where input information from nociceptors is processed in the spinal cord and output nociceptive information is sent to higher centers of the brain involved in the sense of pain. In order to understand how the spinal cord processes signals emanating from nociceptors it is important to identify all the spinal cord inputs and outputs involved in nociceptive signaling. The nociceptor input to the spinal cord comes from dorsal root ganglion (DRG) neurons which enter the spinal cord via Lissauer's tract. Pain and temperature afferents entering through the dorsal roots enter the spinal column and travel one or two segments up or down the cord before penetrating the gray matter of the dorsal horn where they synapse on second order neurons. The trigeminal ganglion (not shown) is analogous to the dorsal root ganglia of the spinal cord and is responsible for painful sensation in the face.

The anterolateral system which is composed of a bundle of fibers located in the ventrolateral aspect of the spinal cord is typically described as transmitting nociceptive and thermal information to higher brain centers. The nerve fibers of the anterolateral system originate from cell bodies of projection neurons in the contralateral dorsal horn which give off axons that decussate via the anterior white commissure. The anterolateral system consists of the spinothalamic tract, spinoreticular tract, spinomesencephalic tract and spinohypothalamic tract. Anterolateral cordotomy, surgical division of the pain-conducting tracts in the anterolateral quadrant of the spinal cord, provides the selective loss of pain and temperature perception several segments below and contralateral to the segment at which the lesion is placed. This procedure is performed on patients experiencing severe pain due to cancer or other diseases for which there are no cure. Although cordotomy is effective in the relief of pain, the effect is usually temporary and pain tends to recur after cordotomies in the form of central pain, that is pain resulting from a lesion or dysfunction of the central nervous system.

The anterolateral system is not the only nociceptive output of the spinal cord. Historically, the dorsal column pathway was not thought to be involved in pain perception. However, data from clinical studies have shown that the dorsal column pathway is involved in relaying visceral nociceptive information. These studies have shown that small lesions, that disrupt fibers of the dorsal columns (see Figure 7-1) that ascend close to the midline of the spinal cord, significantly relieve pain originating in visceral organs. The nerve fibers of these dorsal column neurons originate from the cell bodies of projection neurons many of which are located in the vicinity of the central canal. (Fein, 2012)

Primary hypersensitivity and secondary hypersensitivity



Remember that intense noxious stimuli resulting in tissue damage often lead to an increase in the response to subsequent painful stimuli, called hypersensitivity. Two areas of hypersensitivity are recognized according to their location relative to the site of injury, primary hypersensitivity, an increased sensitivity within the injured area partially due to peripheral nociceptor sensitization, and secondary hypersensitivity, an increased sensitivity in the surrounding uninjured area (see diagram below). A number of studies have shown that primary hypersensitivity involves sensitization to both mechanical and heat stimuli. On the other hand, the area of secondary hypersensitivity is characterized by sensitization to mechanical stimuli only.

Peripheral sensitization versus central spinal sensitization

Peripheral sensitization, (allodynia and hyperalgesia) of nociceptors occurs when the peripheral terminals of the nociceptors are exposed to damaged and/or inflamed tissue and consequently, is limited to the site of injury and/or inflammation. Peripheral sensitization of nociceptors contributes to pain hypersensitivity at inflamed sites (primary hyperalgesia); it appears to play a major role in altered heat but not mechanical sensitivity, which is a major feature of central spinal sensitization.

In contrast to peripheral sensitization, central spinal sensitization, allows low-threshold mechanoreceptor afferents to mediate pain although these afferents do not normally cause pain. In this respect, central spinal sensitization represents a dramatic functional shift in the way we perceive somatosensory inputs: low threshold stimuli which may have been pleasant previously are now painful. In this situation we are experiencing the pain as coming from outside stimuli, although the actual stimuli are not themselves noxious. It is important to keep this in mind because the target for treatment in this circumstance is not the periphery but is actually the central nervous system.

Two forms of mechanical allodynia have been distinguished, one form is called stroking allodynia or dynamic allodynia and is apparent when the skin is gently stroked with a cotton swab. The second form is referred to as punctuate allodynia and occurs when punctuate stimuli such as von Frey probes are applied to the skin. Experimental evidence from patients with complex regional

pain syndrome (also called causalgia and reflex sympathetic dystrophy) suggests that their mechanical stroking and punctuate allodynia is mediated in part by input from large-diameter, rapidly conducting Aβ low-threshold mechanoreceptor afferents (for example see (Gracely, Lynch et al. 1992). This finding does not indicate where in the central nervous system Aβ low-threshold mechanoreceptor input gains access to the pain pathway or where in the pathway central sensitization occurs.

The dorsal horn of the spinal cord is a likely candidate for one of the sites where central sensitization may occur. Moreover, dorsal horn nociceptive specific (NS) and wide dynamic-range (WDR) neurons are the most likely candidates for the neurons in which central sensitization might occur. In order to determine whether central sensitization occurs in either or both of these cell types, responses of WDR and NS dorsal horn neurons projecting into the spinothalamic tract of the anterolateral system were studied in monkeys (Simone, Sorkin et al. 1991). Capsaicin was injected into a location adjacent to the site of mechanical test stimuli to see if the test site exhibited secondary hyperalgesia as a result of the capsaicin injection. The responses at the test site of WDR and NS neurons to the mechanical stimuli were significantly increased, suggesting that increased responsiveness of both WDR and NS neurons contributes to mechanical hyperalgesia produced by capsaicin injection. NS neurons were functionally converted into WDR neurons, that is, they became responsive to low intensity mechanical stimuli. Whereas, WDR neurons simply sensitized, that is, they became more sensitive to the mechanical stimuli they were already sensitive to.

Responses to both innocuous stroking and to light punctate stimuli were either weak or absent before capsaicin and increased dramatically following capsaicin injection. Indicating that both stroking and punctuate allodynia contribute to the allodynia in these neurons. Responses of these WDR and NS dorsal horn neurons to electrical stimulation of the proximal end of severed dorsal rootlets increased significantly after capsaicin injection, suggesting that the hypersensitivity of these neurons is in part due to their increased excitability. These findings support the idea that central sensitization is in part the result of increased excitability of WDR and NS dorsal horn neurons that project into the spinothalamic tract of the anterolateral system.

What is the role of central sensitization in patients with peripheral neuralgia? In a study of patients with unilateral carpal tunnel syndrome, bilateral widespread pressure hypersensitivity was found, suggesting that extensive central sensitization occurred. Presumably as the result of peripheral drive from the injured nerve (Fernandez-de-lasPenas, de la Llave-Rincon et al. 2009).

Central sensitization is a form of functional synaptic plasticity resulting in pain hypersensitivity that is induced by a variety of intense noxious stimuli. The plasticity is evoked by conditioning stimuli that include high-frequency electrical stimulation of C fibers, damaging heat stimuli, and chemical activation of nociceptors by compounds such as mustard oil and formalin, both of which act via TRPA1 in addition to capsaicin, which acts via TRPV1. These stimuli have in common that they are intense and sustained stimuli which activate many fibers. A single painful stimulus, such as a pinch or a needle stick, which does not meet these requirements, will not induce central sensitization.

Central sensitization resembles long term potentiation (LTP) in that it is a long-lasting enhancement in synaptic transmission between neurons resulting from brief bursts of high frequency stimulation. However, LTP is a form of homosynaptic facilitation where it is only the sensitivity of the activated synapses that is changed. On the other hand, central sensitization is a form of heterosynaptic sensitization, where the activity in one set of synapses enhances the activity in nonactivated synapses. This apparently occurs by sensitizing the entire neuron, with the result that NS neurons are functionally converted into WDR neurons, that is, they became responsive to low intensity mechanical stimuli. Furthermore, during central sensitization WDR neurons are sensitized so that they became more sensitive to the mechanical stimuli they were already sensitive to. This change in the responsiveness of NS and WDR dorsal horn neurons is accompanied by an expansion of the spatial extent of their inputs. That is the size of their receptive field increases so that synaptic inputs from silent or ineffective synapses are now effective.

Homosynaptic facilitation is a type of use dependent facilitation of a synapse evoked by activation of that same synapse. Windup as previously described is a form of homosynaptic facilitation in which the response of a dorsal horn neuron to a low frequency discharge of action potentials in C fibers get larger with successive stimuli. As mentioned above both NMDA receptors and NK1 receptors appear to be involved in windup. Moreover, the available evidence from NK1 receptor

knockout mice and using NK1 receptor antagonists shows that activation of NK1 receptors is necessary for wind up to occur. However, in these knockout mice nociceptive thresholds were unaffected as was hyperalgesia.

Disinhibition and central sensitisation

A decrease in tonic inhibition, i.e. disinhibition, of dorsal horn output neurons could account for central sensitization just as well as an increase in the total current carried by AMPA and NMDA receptors in these neurons. In the dorsal horn the amino acids γaminobutyric acid (GABA) and glycine are the major inhibitory transmitters. Both transmitters are present in the synaptic terminals of dorsal horn interneurons and they also coexist in a proportion of those terminals. Experiments in monkeys have shown that inhibition of spinothalamic tract neurons of the anterolateral system by spinal glycine and GABA is reduced during central sensitization (Lin, Peng et al. 1996). This work also suggested that PKC in the spinal cord was involved in the desensitization of glycine and GABA receptors, thereby contributing to the development of allodynia and secondary hyperalgesia that underlie central sensitization.

Experiments in mice have shown that the α3 subunit of strychnine sensitive glycine receptors is predominantly expressed in lamina II of the dorsal horn (Harvey, Depner et al. 2004). Moreover, mice in which the glycine receptor α3 subunit was knocked out showed a reduction in pain sensitization induced by intrathecal PGE2 injection or peripheral inflammation. Therefore, the glycine receptor α3 subunit is a potential target for the treatment of pain.

It is very possible that neuropathic pain and central sensitization may share common mechanisms in the spinal cord. However it should be kept in mind that whereas central sensitization can develop in minutes after an intense noxious stimulus (Torebjork, Lundberg et al. 1992) neuropathic pain typically takes days to develop. Nevertheless it has been proposed that in some cases, neuropathic pain is dynamically maintained by ongoing peripheral nociceptive afferent input which accounts for allodynia, spontaneous pain, and other abnormalities (Gracely, Lynch et al. 1992). Given these reservations remember, that as previously described, the induction of neuropathic pain by peripheral nerve injury results in tactile allodynia. Moreover, in rats peripheral nerve injury also results in a depolarizing shift in the reversal potential of GABA and glycine currents of lamina I neurons in the dorsal horn, causing disinhibition and, in some cases, converting the GABAA receptor and glycine receptor mediated inhibition into excitation (Coull, Boudreau et al. 2003). This might explain the allodynia of neuropathic pain and if something similar happened during central sensitization it might explain the allodynia of central sensitization as well.

The inhibitory neurotransmitters GABA and glycine act on ionotropic, chloride permeable GABAA or glycine receptors or metabotropic (G protein-coupled) GABAB receptors. Under normal conditions the intracellular concentration of chloride ions in neurons is kept low so that the opening of GABAA or glycine activated chloride channels causes the entry of negatively charged chloride ions into neurons thereby hyperpolarizing them. Disinhibition could occur by a shift in the transmembrane chloride ion gradient causing normally inhibitory anionic synaptic currents to be excitatory (Coull, Boudreau et al. 2003).

Pain in the brain

Pain in the brain is outside the scope of this article. Readers are encouraged to not only look at the brain anatomically, but also as a 'brain network'. The functional brain network for pain is being called 'Salience network', it is a FUNCTIONAL network defined only as late as 2012. Lots of analysis of pain in the brain is possible due to the 'salience network'

7. Brain networks in terms of network theory

We first review what is happening in the neural system, in case of chronic stress and burnout. With neural networks we do here NOT mean topograhic networks, but functional networks and effective networks. Acquaintance with the work of Olav Sporns ('Networks of the brains') is recommended. This non-topographical view of neural interactions has been greatly facilitated by quite recent modern mathematics, the small world mathematics of Watts and Strogatz in 1998.

The Default Mode Network, DMN, can be seen as brains operating system. In addition, the limbic system exists, that deals with emotion. In addition, task executive networks exists, as well as higher executive networks. The outside world is mirrored in the brain by the 'mirror neuron system'.

With burnout patients, it is our experience that the cognitive impairment consists of:
– task executive networks that can only be used for limited time
– 'strike' of the higher executive control networks
– a tendency to overactivate the DMN like with 'rumination' and MW, Mind Wandering.

Emotionally, the affect regulation is clearly 'distorted' (which makes therapies as ART, Affect Regulation Therapy, a good candidate for burnout recovery). The amygdala, the memory of long term emotion and fear center, is quicly activitated, upon which fears are projected to the PFC (Pre Frontal Cortex), where anxieties can be 'catastrophised' and result in panic attacks or other 'disproportional' emotional behaviour.

Unfortunately, none of the many brain network imaging facilities has to day investigated the brain networks under burnout. The effect of burnout on brain networks can, however, be deducted from many other states of wich brain networks have been studied – varying from rumination, Mind Wandering up to all neuroscientific states during meditation (2014: 'Meditation – neuroscientific approaches and philosophical implications').

8. Neuroinflammation

With burnout and chronic fatigue syndrom (cfs), since decades some form of (neuro)inflammation has been hypothesised. Nakatomi et al. In 2014 proved this to be the case, very convincingly.

As we saw in part C, in cfs inflammation is promoted, by increased level of the pro-inflammatory IL-6 and decreased level of the anti-inflammatory IL-10.

So far, none of the twenty PET scan centers we approached in Europe were prepared to re-do the Nakatomi empiric research for burnouts instead of cfs-patients. Because of the similarities between

chronic stress and burnout we expect the same findings.

One of the newly researched causes of inflammation are ROS, Reactive Oxygen Species. Strenous exercise can cause ROS and inflammation.

The high IL-10 level found in burnouts and cfs could be interpreted as bodily reaction to (neuro)inflammation, that is caused by ROS (and not cortisol!) Inflammation rather increases cortisol, cortisol downregulates inflammation.

Though the mechanism leading to neuroinflammation has not yet wholly been cleared, the existence of neuroinflammation with cfs has very convingly been evidenced by Nakatomi et al. 2014

Part E measurements

Part B. Enodcrinology

HPA-axis can be measured with:

- **CRF** Corticotropin-releasing factor (CRF) in combination with
- **fMRI neuroimaging of amygdala**

if both are high, it is evidenced the fearful amygdala is overactive (see part B, par. 1.3)

DEX-CRH in combination with low ACTH1-24 Syncthen test.

An improvement of the DST is the DEX-CRH test (dexamethasone-corticotropin releasing hormone test). Here, the HPA axis is re-tested after prior administerd suppression. The paradgim is desigend to test joint pituitary and adrenal cortex reactivity.

The DEX-CRH test should preferably be followed by a low dose ACTH1-24 Synachten test. In contrast to the DEX-CRH test, the Synacthen test is used to trigger immediate cortisol secretion from the adrenal cortex. Therefore with application of the low dose synthetic ACTH, the response sensitivity of the adrenal cortex can be tested pharmacologically (Flandreau et al. 2011). And: the presumption of a 'adrenal fatigue' can be tested pharmacologically.

A dysfunctional HPA-axis is evidence of at least chronic stress, and is very likely to occur in burnout and chronic fatigue syndrom as well.

Measurements to the than HPA-axis,
In addition, cfs and therefore likely also burnout can be evidenced by:

- **TH secreted by thyroid gland (ELISA)** at the pinal gland (part B, par. 4) and
- **T3 T4 ratio** at the thyroid gland (part B, par. 2)

Measurements in vivo of the adrenal gland are difficult in vivo, therefore supposed 'adrenal fatigue' at the adrenal glad does not generate measures in this overview.

Part C Immunology

Chronic stress and therefore also very likely burnout and chronic fatigue syndrom can be evidenced by simultanous

- increased level of the pro-inflammatory IL-6 and
- decreased level of the anti-inflammatory IL-10 (see part C, par. 2 and par. 3)

In addition, cfs can be measured by the symptoms of increased oxidative stress and altered muscle excitability (Yammers 2005)

Part D Nervous system

With chronic stress, the amygdala is overly activated (also during attempts to sleep) and, relatedly,

in insomniacs the hippocampus is often found te be 10-20% smaller.

The overactivity of the amygdala, as well as smaller hippocampus, can be neuro-imaged as proof of chronic stress/burnout (chronic precedes burnout).
Another biomarker of chronic stress is chronic insomnia; to the chronic stressors of regular life, a traumatic experience is being added: that of insomnia, not falling asleep for nights in a row.

(sleeping pills are strongly recommended to minimize the 'insomnia fear'; once starting taking sleeping pills, it is the challenge to reorganise life to not-chronic-stress , after which the sleeping pills can be decreased in administration).

With prolonged chronic insomnia, secretation of sleep hormones as melatonine and adenosine are radically reduced. One does not get the normal 'warning for sleep anymore', consisting of a feeling like 'I want to shut down everything'. Tired muscles and tired nerves do not induce sleep; the great 'switch', the VLPO in the hypothalamus, is supposed to release natural GAGA ligands, to bind enough neurons so that less than 100.000 remain active, after which sleep may fall in.

When, due to chronic 'hypervigilant state' hypothalamus and VLPO do not anymore secrete natural GABA ligands, sleeping pills are required (like BZD, Benzodiazepines) in order to bind GABA receptors.

Sleep deprivation of rodents leads to death within appr. 20 days. For humans, unfortunately, no statistics are available. A hypervigilant, insomnia traumated human never returns to normal sleep rhytms without medication. This is very severe.

Chronic fatigue measurements (within D, neural system)

There are so many cfs measurements possible (within part D, neural system), that we prefer not to repeat them here. The reader can find measurements integrated in the article. Measurement methods of cfs deserve an article of their own.

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