

Topics

1. Psychologic Stress and HPA axis
2. Neuroanatomy of stress
3. Psychologic stress and wounds
4. The Brain Skin Axis and Inflammation
5. Itch in wounds and stress
6. Reducing stress to improve wound healing with therapies targeting the brain
7. Future directions

Wound healing and stress

Chronic, low-grade stress and the inflammation associated with it, are underlying factors in most chronic illnesses.

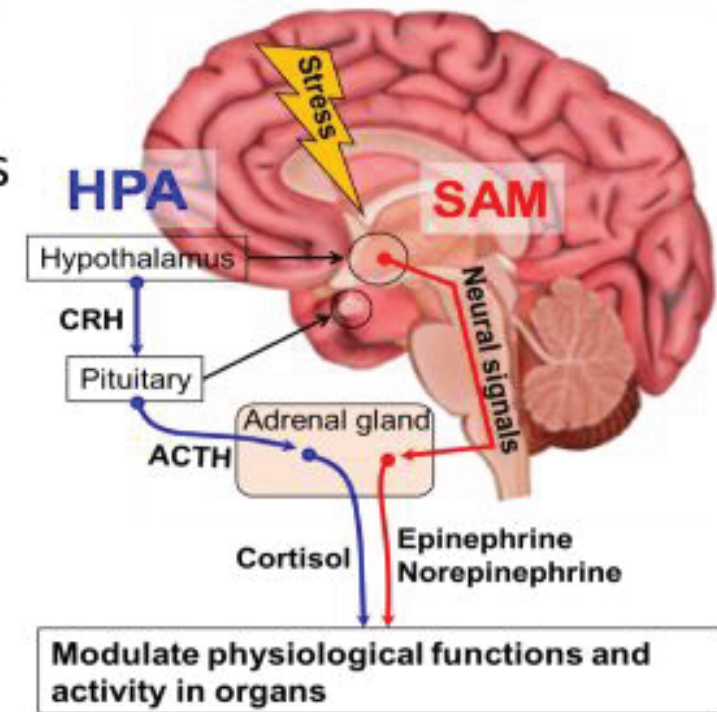
(Such as cardiovascular disease, type 2 diabetes, metabolic syndrome, obesity, autoimmune disorders, Alzheimer's, asthma, arthritis, and many types of cancer.)

Chronic stress and inflammation are all the more dangerous because it can take years or even decades before the first symptoms of disease appear.

Psychologic Stress HPA and SAM

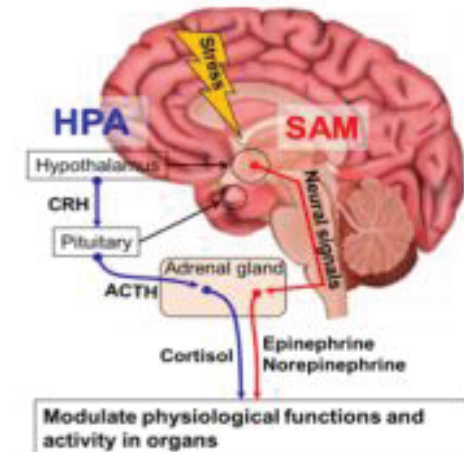
- The hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary (SAM) axis are major descending stress-response pathways

Fig. 1. Responses of HPA and SAM to stress



Physiology of Stress

Fig. 1. Responses of HPA and SAM to stress



- Stress upregulates secretion of corticotrophin releasing hormone (CRH) from the hypothalamus, which facilitates release of adrenocorticotrophic hormone (ACTH) from the pituitary.
- ACTH increase secretion of cortisol from adrenal gland
- The SAM axis responds to stress by sending neural signals from the hypothalamus to the adrenal gland by sympathetic nervous system, increases the secretion of epinephrine and norepinephrine

Psychologic stress and skin diseases

- Using a validated Perceived Stress Questionnaire (PSQ; 9) a 30-item questionnaire that measures self-reported stress we found that multiple skin diseases are highly associated with high stress levels in large cross sectional studies in College students and Med school students in USA, Australia and Saudi Arabia .
- Common association with eczema, psoriasis and itch, skin barrier repair

Bin Saif et al. Saudi Med J. 2018 Jan;39(1):59-66. Stewart et al..Australas J Dermatol. 2018 Feb. : Schut et al. . Acta Derm Venereol. 2016

Stress Impairs Wound Healing By as Much as 40%

Induces Glucocorticoids and Catecholamines

Glaser et al: Arch Gen Psych 1999;56:450-456.
Marucha et al: Psychosom Med 1998;60:362-365.
Padgett et al: Brain Behav Immunol 1998;12:64-73.
Kiecolt-Glaser et al: Lancet 1995;346:1194-1196.

Stress alters cutaneous permeability barrier homeostasis

- Stress stimulates increased production of glucocorticoids,
- In-turn, adversely affects permeability barrier homeostasis
- Stress affects the immune system

Denda et al. Amer J Physiol 2000, Christian et al. Neuroimmunomodulation 2006

Stress levels in pts with chronic wounds

- Patients with leg ulcers demonstrated higher stress and anxiety levels in comparison with healthy participants.
- This could be explained by the associated stressors of living with leg ulcers, including pain, self-esteem loss, and social isolation, with subsequent negative emotions that could potentially lead to anxiety and stress and a vicious cycle

Hamer J Wound Care. 1994;3(2):99-101.

Chronic wounds and depression

- Depression is a very common comorbidity in patients with chronic wounds.
- At least 30% of those patients suffer from depressive symptoms or anxiety.
- Depression is often associated with wound duration, odor of wounds, and furthermore with pain and immobility.
- Depression might reduce wound healing itself via psychoimmunological effects.

Renner et al. Chronic Wound Care Management and Research 2017

Stress and Biopsy induced wounds

- Healing of biopsy induced wound took significantly longer (25% - 40% longer) under stressful conditions as compared with under non-stressful conditions.
- which may be associated with altered immune activity due to stress (e.g. Significant reduction of IL-1 β) (

Kiecolt-Glaser et al., Lancet, 1995; Phillip et al., Psychosomatic medicine, 1998).

The Affective Component of Stress Reduces Quality of Life for Chronic wound Patients

- Chronic wound is associated with higher rates of:
 - Mental distress
 - Psychiatric diagnosis
 - Anxiety
 - Depression
 - Suicidal ideation
- These affective symptoms have major impacts on quality of life

Mechanism of Stress Effect on Wound Healing

- Proinflammatory cytokines play a critical role in the healing cascade in particular interleukin-1 α (IL-1 α), IL-1 β , IL-6, IL-8 and tumor necrosis factor- α (TNF- α).
- In addition, cytokines regulate the ability of fibroblasts and epithelial cells to remodel damaged tissue
- Stress Reduces proinflammatory cytokines that are key to successful healing preventing infection, prepare injured tissue for repair, and
- In IL-6-deficient mice exhibit up to a **3-fold greater** healing time as compared to healthy wild-type

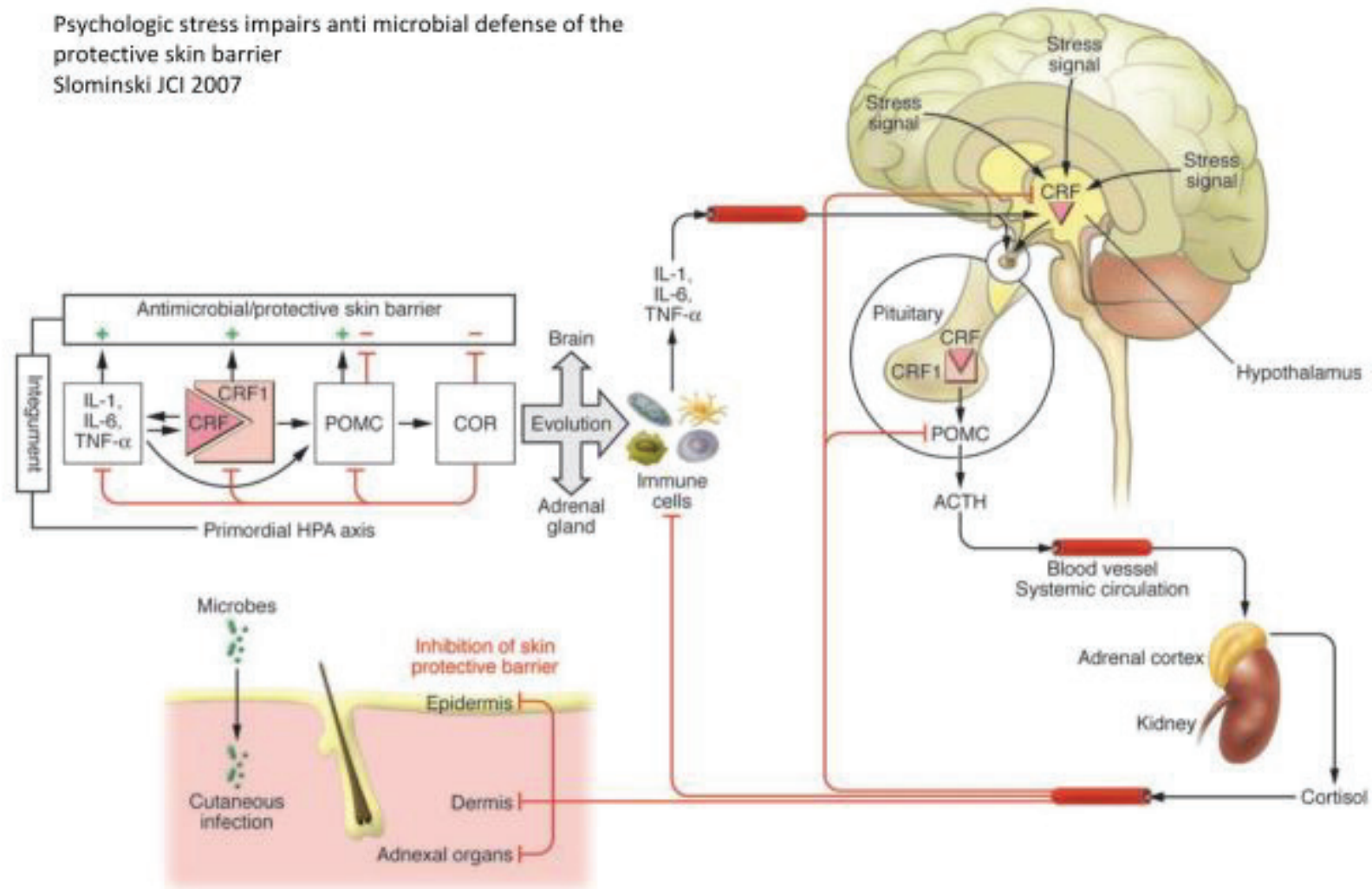
Gallucci et al. FASEBJ 2000;14:2525–2531

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Denda et al. Amer J Physiol 2000, Christian et al. Neuroimmunomodulation 2006

Psychologic stress impairs anti microbial defense of the protective skin barrier
 Slominski JCI 2007



Reduced Oxytocin and Vasopressin and wound healing

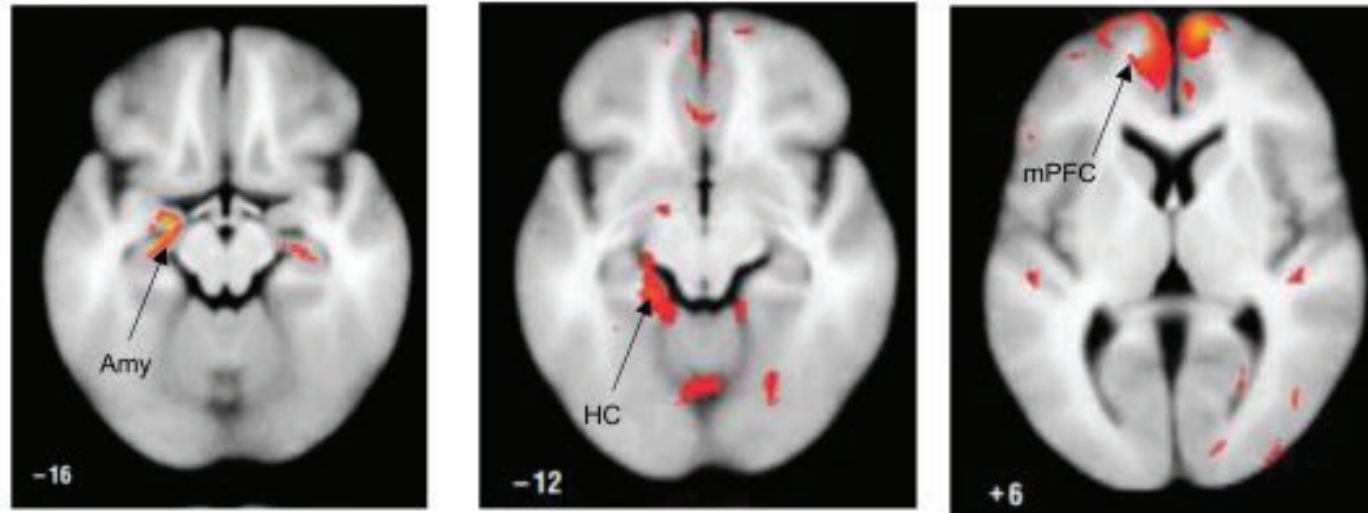
- Studies in couples on wound healing sites in the forearm
- Slower healing was noted in those with lower oxytocin and vasopressin levels.

Gouin et al. Psychoneuroendocrinol 2010

Brain and Skin Wounds

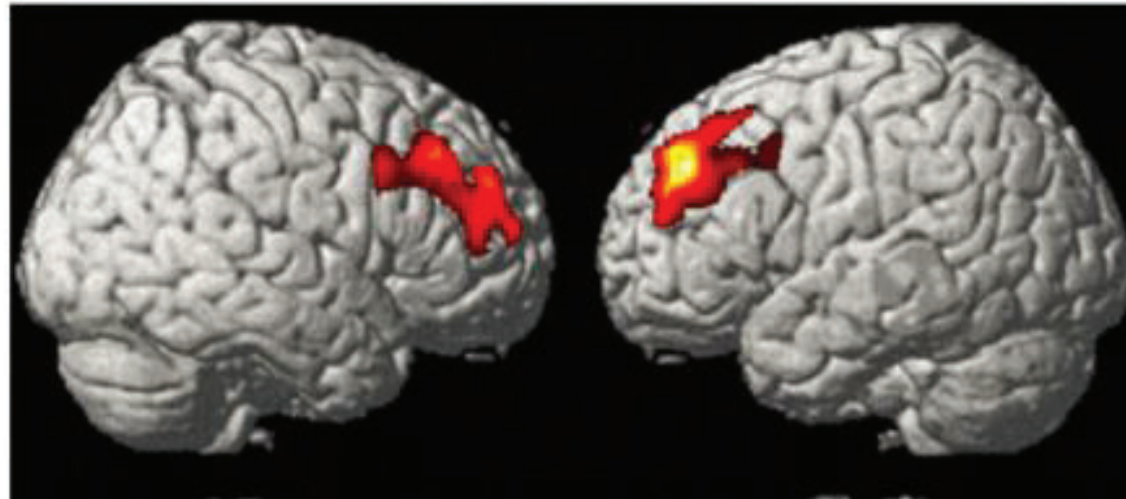
Negative psychological factors due to chronic wound may affect key brain regions regulating the HPA axis, which alter a variety of physiological activity including the immune function, resulting in delayed wound healing or aggravation of chronic wounds.

Negative psychological factors affect structures of key regions regulating the HPA axis, which can cause dysfunction of the HPA axis.



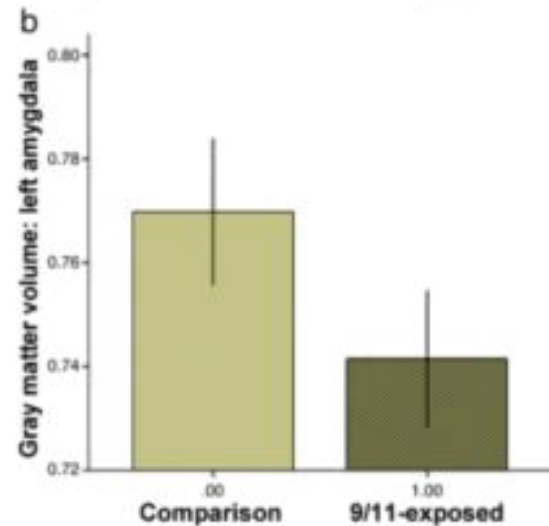
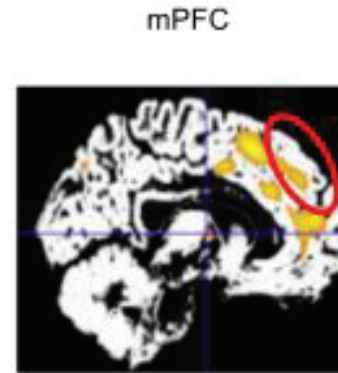
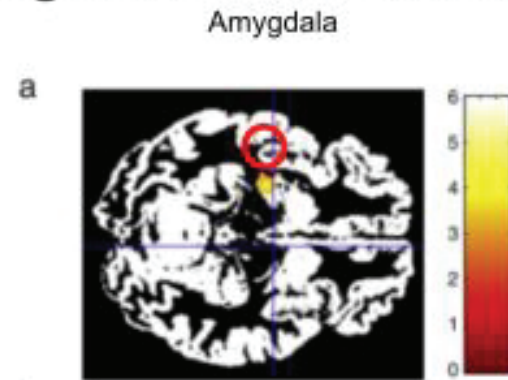
Reduced volumes of key brain regions regulating the HPA such as the amygdala, mPFC, and hippocampus in depression (Frodl et al., Arch Gen Psychiatry, 2008)

Negative psychological factors affect structures of key regions regulating the HPA axis, which can cause dysfunction of the HPA axis.



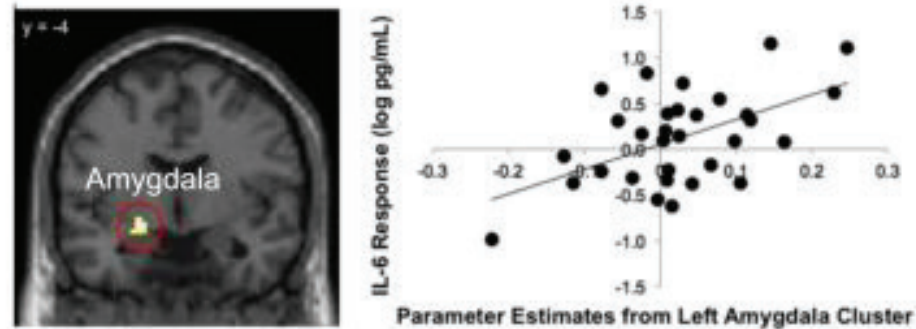
Reduced PFC volume in Chronic fatigue subjects (Okada et al., BMC Neurol. 2004)

Negative psychological factors affect structures of key regions regulating the HPA axis, which can cause dysfunction of the HPA axis.



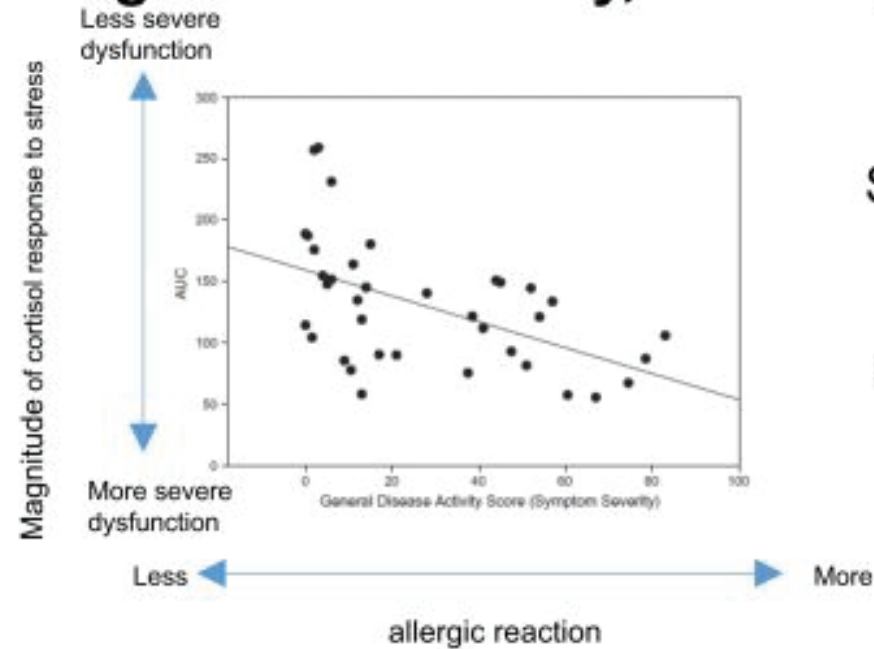
Comparison of brain volume between healthy adults within 1.5 miles of the World Trade Center on 9/11/01 (9/11-exposed) and those living more than 200 miles away at the time Data were collected between 41 and 48 months after 9/11/01. Greater reductions of volumes in the amygdala and mPFC in 9/11-exposed group (Ganzel et al., NeuroImage, 2008).

Stress-related immune reaction in the periphery is associated with activity in the amygdala



Psychological stress increases activity in the amygdala sending excitatory signals to the hypothalamus to activate the HPA axis.
Immune response to psychological stress in the periphery is greater in healthy subjects with greater amygdala response to the stress
(Muscatell et al., Brain, Behavior, and Immunity, 2015)

Dysfunction of the HPA can affect a variety of physiological functions including immune activity, resulting in aggravation of inflammation.



Severity of allergic rhinitis is greater in patients with greater dysfunction of the HPA (Buske-Kirschbaum et al., Brain, Behavior, and Immunity, 2010)

Wounds and Itch

- Burn injuries and especially scars cause significant chronic itch with significant impaired QOL
- Itch in keloids major problem associated with neuropathic damage
- Epidermolysis bullosa Dystrophica a rare genetic disorder causing blistering causes severe chronic itch with the wounds
- Venous ulcers are commonly associated with itch

Parnell Wounds 2018, Lee et al. JAAD 2004, Goldschnieder et al. BMC MED 2013, Paul Adv Skin Wound Care 2013

Stress and chronic itch in Wounds

- Stress impacts itch
- Patients with chronic itch have significant sleep abnormalities this further increases stress
- Decreased sleep impairs wound healing
- Aggravates scratching that further damages the skin barrier

Lavery et al. Acta Derm Venereol 2017, Lavery et al. Int J Mol Sci 2016, Patel et al. Acta Derm Venereol 2007,

The Itch-Anxiety Cycle

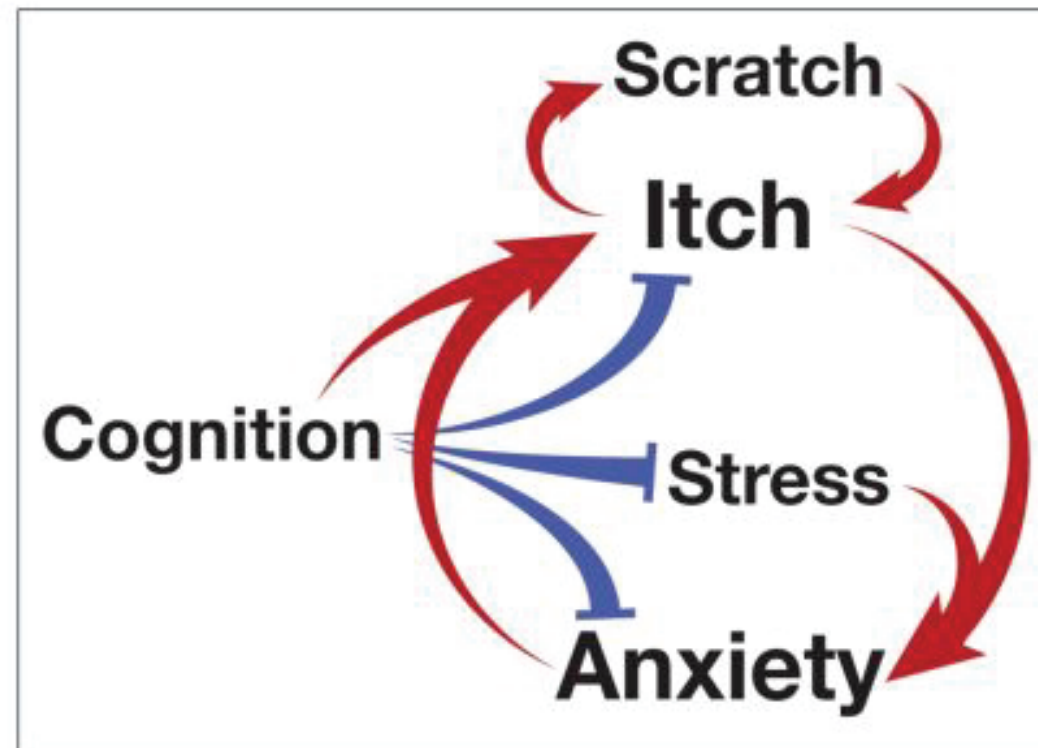
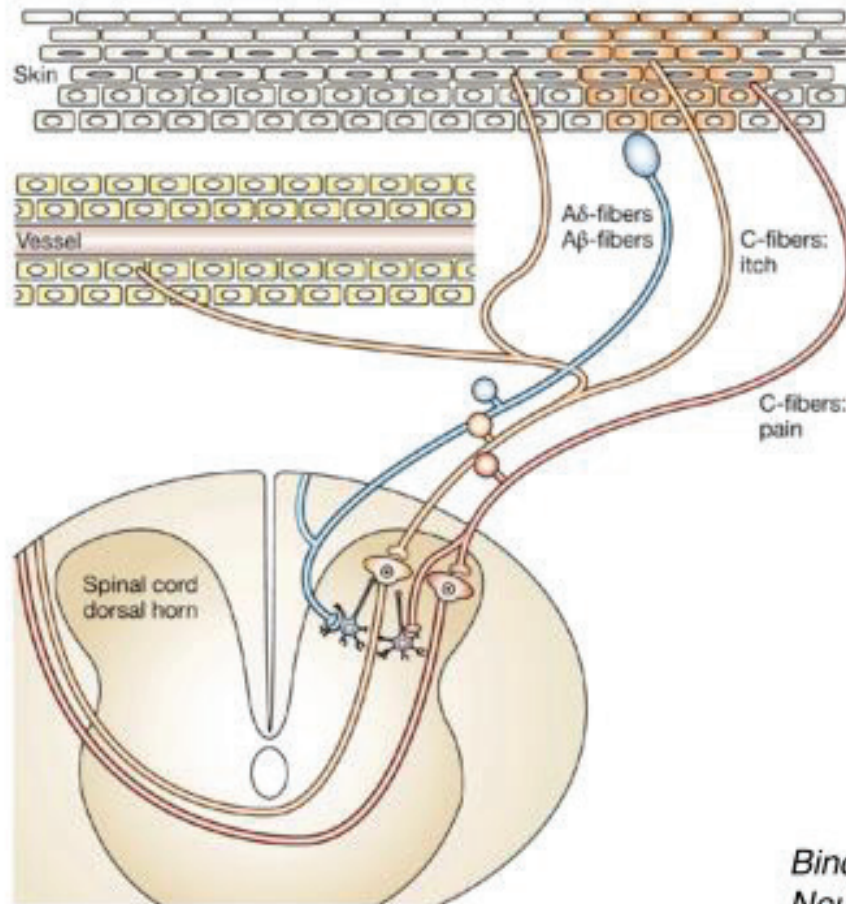
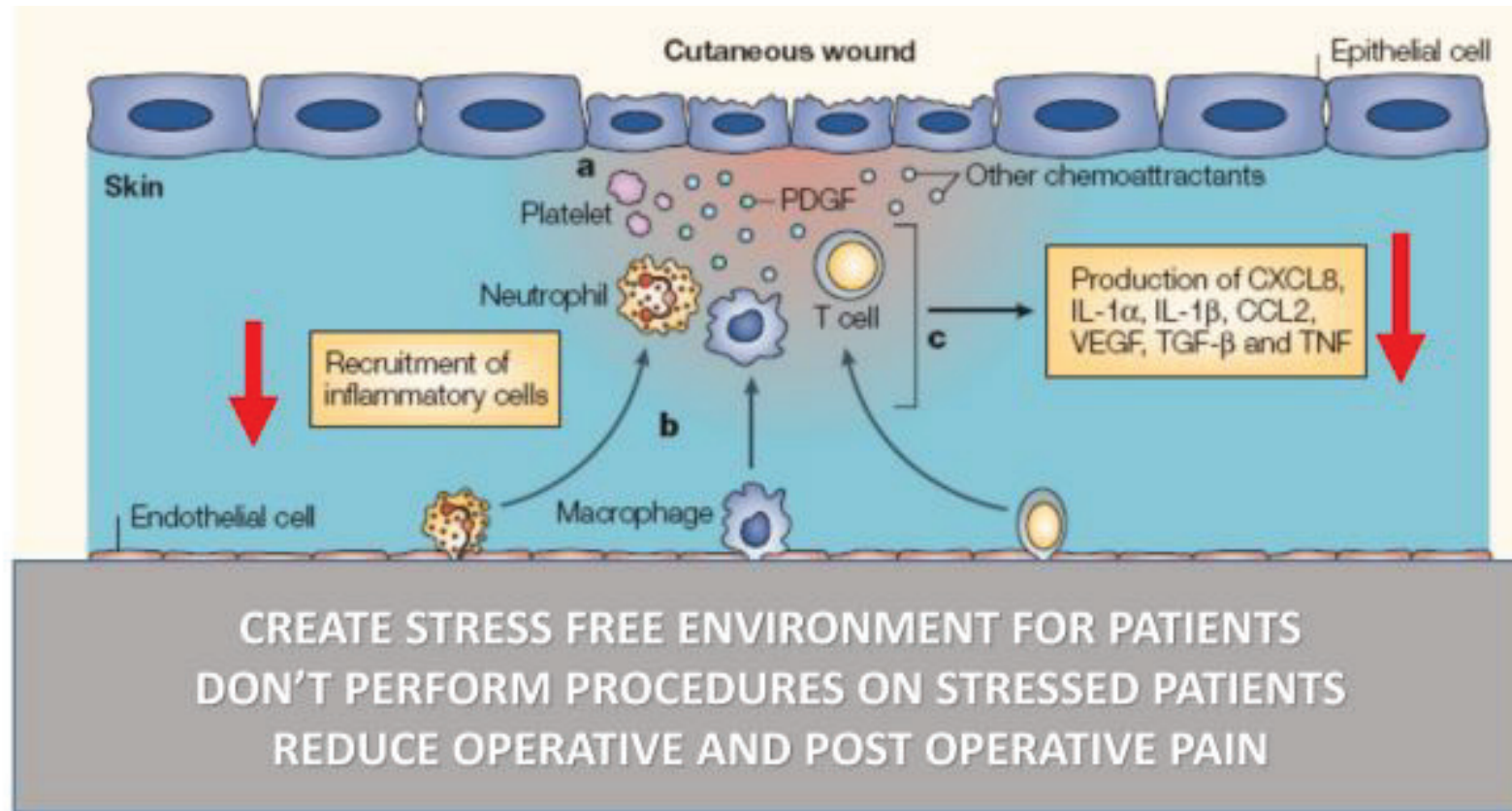


Figure by Hjalte H. Andersen

Peripheral and central itch sensitization



Binder A, et al. *Nature Clinical Practice Neurology* 2008; 4: 329-337



Worrying about Surgery
Depression
Negativism
Isolation
Postoperative Pain

Physical and Mental Exercise
Positive Attitude
Social Interaction
Pain Reduction
Oxytocin

Meta analysis of studies on interventions to reduce stress for wound healing

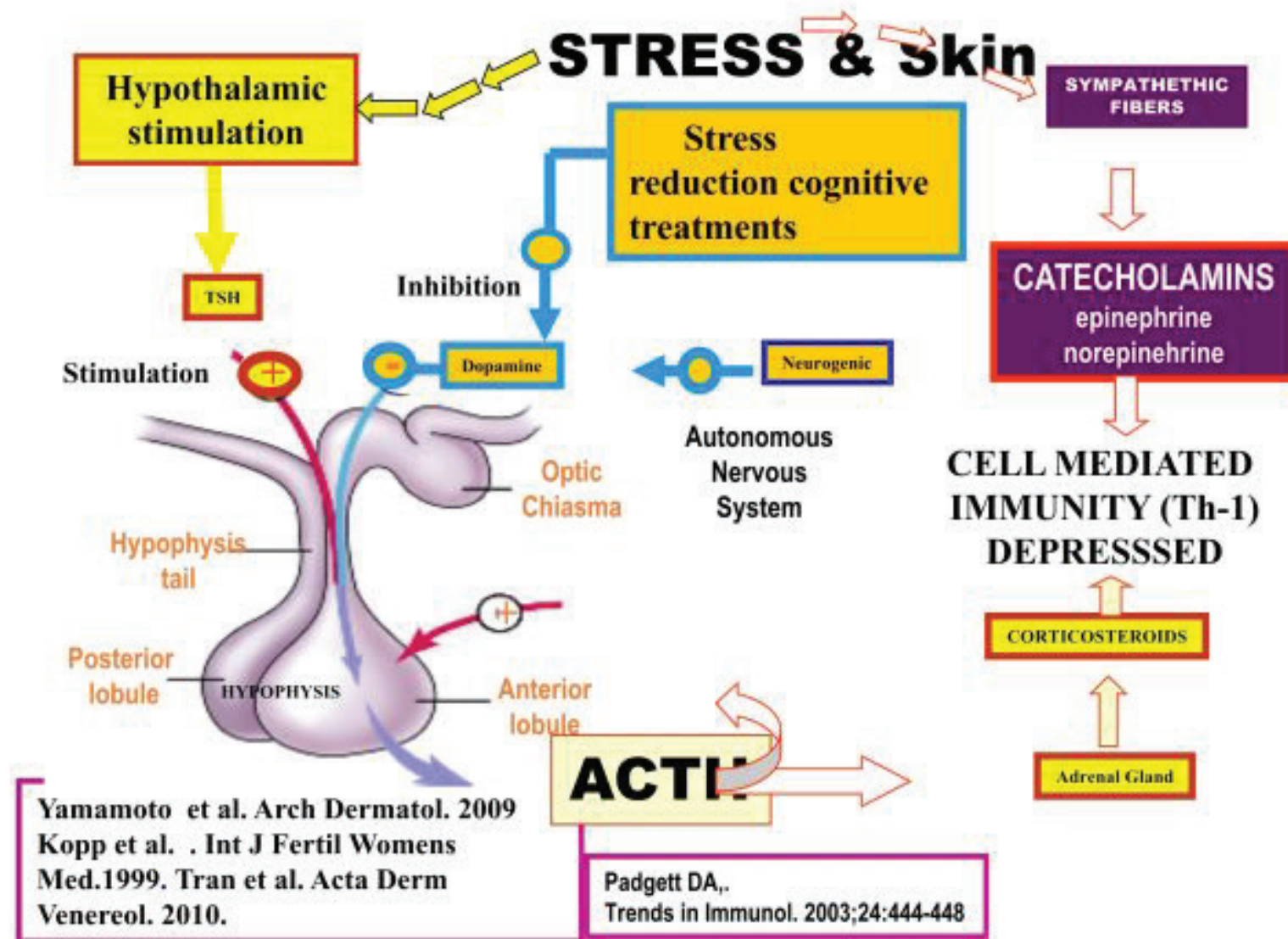
- Decreased levels of cortisol, epinephrine and norepinephrine (stress-related hormones) were associated to interventions :
- yoga, meditation, tai chi
- mindfulness,
- religious/spiritual practices,
- cognitive behavior therapy, coping
- Physical exercises
- Acupuncture

Moraes et al. Psychol Health Med. 2017
Dec20:1-18

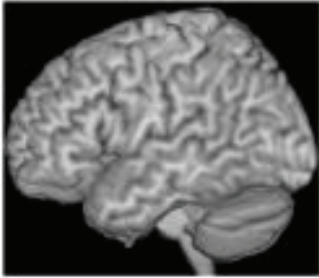
Increased Vasopressin and Oxytocin improves wound healing

- Supportive marital interactions increase vasopressin and oxytocin levels in subjects with wounds
- Modulates the stress response, and subsequently wound healing is promoted

Gouin et al. Psychoneuroendocrinol 2010



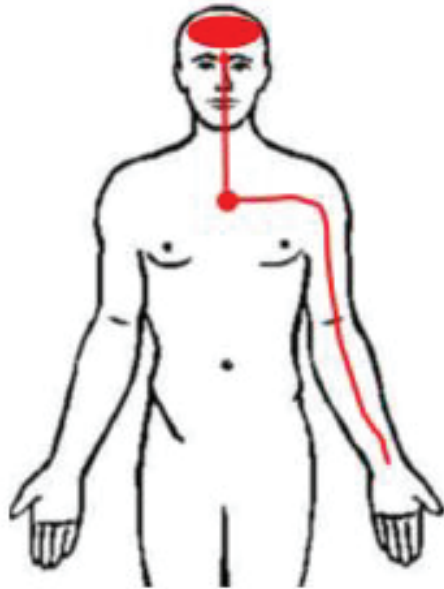
Target the brain for Wound healing



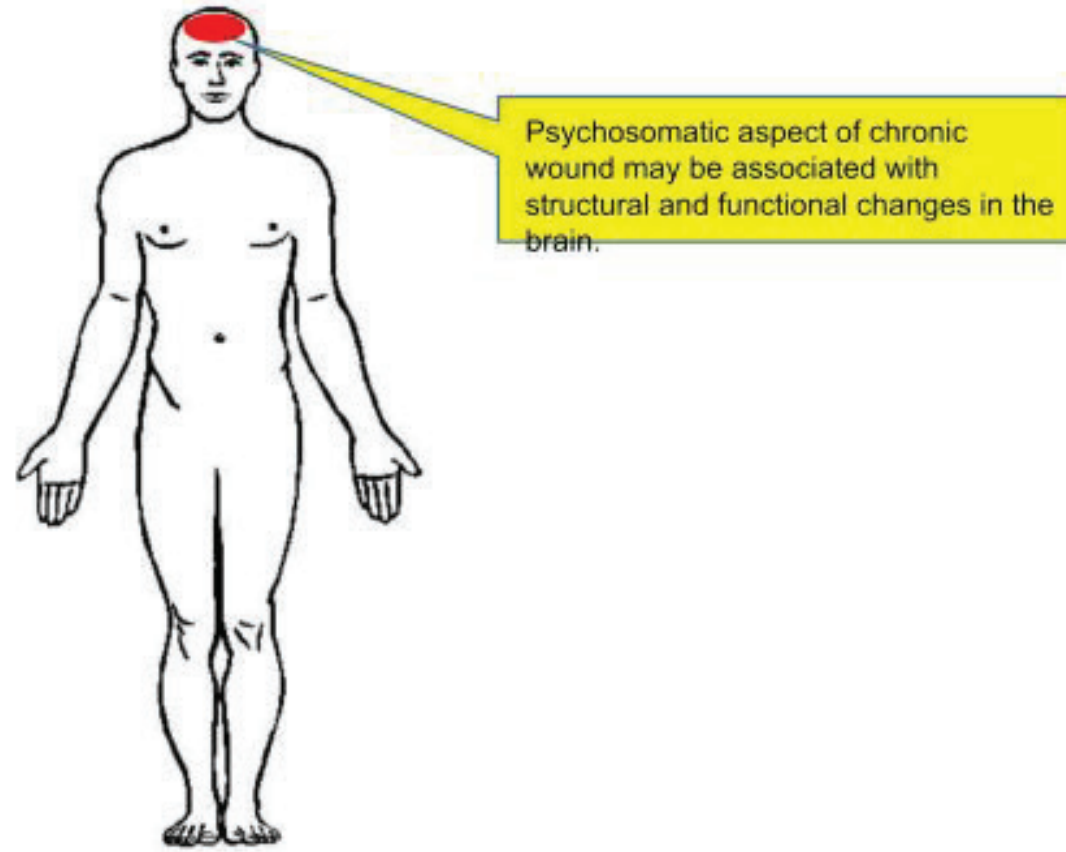
- While the wound is in skin the brain can reduce stress and improve wound healing



By Top down approach



Chronic wound may affect functions and structures in the brain



Effect of Stress on Hypothalamic Volume in patients with atopic eczema

Fig.2. Correlation analysis of the hypothalamic volume and stress

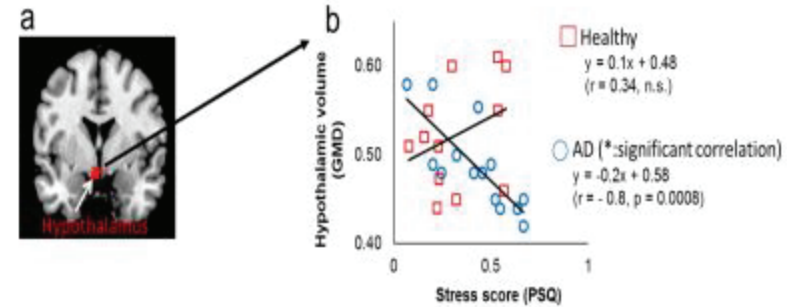
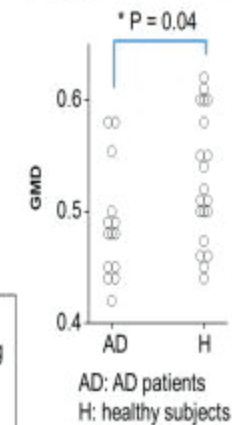


Fig. 2: Structure MRI data was analyzed using Voxel-Based Morphometry 8 (VBM8). VBM8 is a reliable software used by many researchers to investigate anatomical changes in the brain including small structures such as the hypothalamus⁷⁰⁻⁷³. As shown in Figs. 2a and b, the GMD in the hypothalamus showed a significant and negative correlation with PSQ in the AD patient group (family wise error corrected $p < 0.05$ with small volume correction (10 mm radius of sphere)). Confounding factors, such as age and individual differences in whole brain volume, and effect of disease duration were covariates out from the analysis.

Fig.3 Comparison of the hypothalamic volume



Potential therapy for wound healing by targeting the brain

CNS targets for stress reduction and sensitization treatment



- GABA: gabapentin, pregabalin
- Other neurotransmitters: mirtazapine 15 mg
- Combo: mirtazapine and gabapentin/pregabalin
- NK-1 inhibitors

Stull & Yosipovitch Exp Opin Pharmacotherapy 2016
Tey & Yosipovitch Br J Derm 2011

Acupuncture for wound healing and stress reduction

1. Acupuncture of L11 in the elbow has been shown to reduce stress and improve itch
2. Recent large study analysis shows it improved wound healing from burns



Tey et al. Clin Dermatol 2013

Paſb et al. Dermatol Therap 2013

Loskotova . Burns. 2017 Dec

Healing Touch Treatment

- Healing Touch - bio field therapy
- (HT) has been reported to relieve pain, stress, and anxiety and itch

Danhauer SC, et al . J Soc Integr Oncol 2008; 6: 89-97.

Kemper KJ,. J Soc Integr Oncol 2009; 7: 12-8.

Curtis J. Amer Acad Dermatol 2011

New Venues for treatment for improvement of healing wounds

- Shorter hospital stays and lower analgesic use amongst patients in hospital rooms with a view compared with no view
 - Patients who have roommates have shorter hospital stays compared with those in single rooms
 - May improve physiological functioning reduce epinephrine and increase in oxytocin and wound healing.
- Therefore interventions designed to enhance social support and reduce stress help in wound healing

Wicke Wound Repair Regen 1995. Ulrich, Science 1984;. Kulik J Pers Soc Psychol 1996;