The Strauss-Kahn Syndrome

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Abstract

Accumulating evidence shows that the central nervous system (CNS) regulates the activity of the immune system. Concerning the role of immune system in cancer, psychosocial influences on immune function provide a **mechanism** of association between psychosocial factors (like interpersonal aggression) and cancer prognosis. Social conflicts between males, involving high aggression stress and threat (psychosocial conflicts) produce both an allostatic state and allostatic load. The costs for aggressors (Hawks) and victims (losers) tested under semi laboratory conditions are quite different. Testosterone does not cause aggression, only exaggerates the pre-existing pattern and response to environmental triggers of aggression. The individual's personality type (authoritarian Hawk or Dove) has major impact on psychoneuroimmune mechanisms linking aggression stress through inflammation to cancer. Due to the latest connotations we propose this personality phenomenon label as "the Strauss-Kahn syndrome".

Key words: Aggression stress, the allostatic load, testosterone, DHEA, type A personality, HPG-axis, inflammation, NF κ B, IL-6, Stat3, carcinogenesis

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Introduction

Unemotional violence associated with **aggression stress** is often called **'predatory'** because it involves a restricted intention signaling, low emotional/physiological arousal, and decreased glucocorticoid production. It covers a structural similarity at the level of **the hypothalamus,** where the control of **affective** and **predatory aggression** diverges. Sham and ADXr rats were submitted to resident/intruder conflicts and the resulting neuronal activation patterns were investigated by **c-Fos immunocytochemistry.** Aggression stress activated **the mediobasal hypothalamus,** involved in predatory aggression was markedly larger in ADXr rats, c-Fos counts correlated positively with the share of vulnerable attacks and negatively with **social signaling.** Glucocorticoid deficiency increased c-Fos activation in **the central amygdala,** also involved in aggression. Activation patterns in **the periaqueductal gray** (involved in autonomic control) also resembled those seen in **aggression.**[27] These findings suggest that **antisocial** and **predatory aggression** lead to similar **stress** and are controlled by **overlapping neural mechanisms.**[21]

N Power means power-motivated individuals

N Power means power-motivated individuals concerned with having impact over others, and they derive **reward** and **reinforcement** from having this impact. Power-motivated individuals are more likely to be successful in **managerial** positions with vibrant careers. They tend to be perceived by others as competent. They also tend to make **autocratic decisions.** Power-motivated individuals take **bigger risk** in **gambling** situations to garner attention. They are also more likely to be **violent** with their significant others, to **abuse** alcohol (drugs) and to be **sexually promiscuous.** Power-motivated individuals are **coded** to take strong and forceful actions that have impact over others, controlling, influencing others, offering advice, impressing others sexually, they need to achieve fame, prestige and reputation, and actions that elicit a strong emotional response in others.

Testosterone and risk-taking behavior

Testosterone is positively associated with **risk-taking behavior** in social domains (crime, aggression). The scant research is **linking** testosterone to **economic risk** preferences (risk preferences, ambiguity preference, loss aversion). Individuals with **low** and **high** levels of testosterone are risk and ambiguity **neutral,** while individuals with **intermediate** levels of testosterone are risk and ambiguity **averse.** These results provide evidence for a **nonlinear** association between **economic preferences** and levels of endogenous **testosterone.** High-levels of endogenous testosterone were positively associated with choosing less frequently from advantageous Iowa Gambling Task (IGT) descs of cards, indicating **greater risk taking.** High levels of testosterone are associated with willingness to greater risk in **both** sexes. [22]

Authoritarian personality, aggression and dominance

N Power is positively correlated with baseline **testosterone,** suggesting that high baseline levels of testosterone manifest an **authoritarian** individual's **personality.** N Power positively predicts mane of **the dominance** behaviors that high levels of testosterone are associated with: entering influential occupations, drug abuse, spousal abuse, risk taking, and **sexual promiscuity.** These findings suggest that there is a **functional link** between n Power and individual differences in testosterone levels. N Power and testosterone is positively correlated and is shaped by many factors: asserting **dominance,** parenting styles, and heritability, in addition to biological factors like testosterone. In a randomized, placebo-controlled study it was found that men treated with testosterone had both **increased aggression** and symptoms of **mania** when compared to controls. Prisoners with high testosterone tend to have a history of **violent crime** and their behavior is **more aggressive.** When behavior ratings are derived from observers, positive relationships between testosterone and **dominance** or **aggression** are consistently observable. These and many other findings document that, high levels of testosterone **promote** the pursuit of **dominance** and status in socially acceptable ways, but in some cases they can also lead to **aggression, antisocial behavior** and this type of behavior we propose to label as **the Strauss-Kahn syndrome (SKS).** More extreme cases can have also a character of **violent crime.**

Reward-reinforcing automata

When using dominance contest methods with experimentally-varied outcomes, studies found that n Power predicted testosterone increases after a contest **victory** and testosterone decreases after a **defeat.** In one study, the mere anticipation of a dominance victory was sufficient to make power-motivated men's testosterone levels arise. Other methods of arousing n Power, as watching movies depicting dominance, also drive increases in testosterone. Testosterone increases promote the engagement in another dominance contest and lower the threshold for **aggressive** engagement, a conclusion that is supported by both animal and human studies. In mammals, engagement in another dominance contest can be to one's benefit after having **won** a contest, what is allowing further to ascend in **dominance hierarchy** through **winning** as **facilitated** by physiological and learning enhancements. In rats, testosterone increases have also been **linked** to **reward** and **reinforcement.** In mice testosterone surges after **winning** contests can act as **reinforcers** for effective dominance until an **automata-like** behavior. Human research also shows that **wictory**-induced testosterone increases predict better implicit learning of behavior that was instrumental to winning dominance contests. Decreases in testosterone as a **function of losing** make subject less motivated to engage in dominance contest and do not reinforce antecedent behaviors. After **losing** a dominance contest, decreases in testosterone make it less likely one will expend more energy on the costly pursuit of power. In mice, testosterone increases as a **function of winning** dominance interactions, and **the likelihood** of future wins in dominance contests

strongly increases after a series of testosterone-increasing wins. It suggests that testosterone increases also have a **reinforcing** effect on dominance pursuit. Contest-induced testosterone increases predicted men's inclination to **engage** in another contest, while testosterone decreases predicted men's behavioral **withdrawal** from dominance situations.

Winners versus losers

Research on the biological components of n Power arousal examined the activation of **sympathetic nervous system** as a **function of n Power arousal.** Men high in n Power and high in **activity inhibition** had elevated levels of epinephrine in response to the power challenges. Activity inhibition as a measure of self-control is associated with **right-hemispheric brain functions** including **HPA-** and **SAM-axis** regulation. In humans and other mammalian species, **cortisol** acutely rises in response to situations perceived as **uncontrollable** and **stressful.** Cortisol levels changed as an **interactive function** of both the contest outcome and their n Power. Higher levels of n Power were associated with a greater cortisol increase in **losers** and a greater cortisol decrease in **winners.** Baseline levels of testosterone predicted cortisol changes after dominance contest, in which high-testosterone men who **lost** had cortisol increases and those who **won** had cortisol decreases. It means that baseline testosterone is a marker of dispositional power, or n Power. **The stress** of power-motive frustration via losing drives **cortisol** increases selectively in power-motivated individuals. Probably individual differences in n Power are similar to dominance ranks in animals. The power-motivated humans often behave in dominant ways similar to high-dominance members of other species as reflected in **higher aggression, risk-taking,** and **sexual activity.**

Frustrated n Power: link to immune system impairment

By placing such experiments in a broader context, exploration of changes in real-life outcome behaviors as a function of testosterone or estradiol change in response to dominance contests bolster this research line with greater **ecological validity.** Exploration of potential relationship between frustrated n Power, cortisol, depression and **carcinogenesis** is also an important path of this new research. **Frustrated** n Power has been **linked** to **immune system impairment, inflammation** and **cancer.** The positive **link** between n Power frustration and cortisol release extend this line of research into exploration of correlations **psychopathology** with **carcinogenesis.**[23] In a **neuropsychological perspective,** fMRI gives a promise for the examination of the neurological basis of individual differences, and researchers in **personality neuroscience** are beginning to exploit this tool. There are published studies examining **the moderating** role of n Power on patterns of **brain activation.** The hypothalamus is active in control of hormone axes (hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal), as well as dominance behavior. Studies of dominance use neuroimaging to measure the relationship between **brain activation of the hypothalamus** and its connection with other parts of **the emotional brain** and subsequent hormone release as a function of n Power. The aim is to uncover how **the brain orchestrates** the complex hormonal responses to **dominance** challenges, **stressors, inflammation,** and **cancer.**

Higher ambiguity – lower winning probabilities

Ambiguity aversion is a very strong and puzzling phenomenon: in the normative sense it seems irrational, in the practical sense it leads to **highly disadvantageous** results in many social domains including **health, finance** and administrative issues. It was found higher activity for **ambiguous** games in **the orbitofrontal cortex (OFC), inferior frontal gyrus (IFG), anterior insula,** and **posterior parietal cortex.** Activity in IFG was correlated with the level of ambiguity aversion, and this area has a role in the process of **resolving** ambiguity.

Examining the representation of risk and ambiguity is therefore of interests for understanding **the neural processing of uncertainty** in relation to **aggression, dominance, stress, inflammation** and **carcinogenesis.** For example, an adjacent area in **left OFC** exhibited higher activation levels for **higher ambiguity** levels as well as for **lower winning probabilities.** Both **the striatum** and **the medial prefrontal cortex (MPFC)** receive reward-related **dopaminergic** inputs from **midbrain** neurons that encode **the reward prediction error (RPE)** as the difference between the received and expected reward. The free-energy formulation of **false inference** can be used to explain positive symptoms in **addiction** of **alcohol, drugs, power** and **sexuality. The MPFC** is reciprocally connected to **the posterior cingular cortex (PCC),** and both are parts of **the brain's default system,** which attend to internal body and mental states. [20]

Inference machine

In theoretical and computational neuroscience we can focus on Helmholtz's suggestion that the brain is an **inference machine.** This idea is now a fundamental premise in **neurobiology.** Above framework assumes that the brain uses internal hierarchical models to predict its sensory input and suggests that neuronal activity (and synaptic connections) try to **minimize** the ensuing **prediction error** or **free-energy.** This free-energy is a measure of **surprise** and essentially the amount of prediction-error. In both accounts higher cortical areas **organize** activity of lower-levels through **suppression** of their free-energy. Of particular interest here is the so called **'default-mode network' (DMN),** a network of regions that show high metabolic activity and blood flow at rest but which **deactivate** during **goal-directed cognition.** [8] We associate **failures** of top-down control with non-ordinary states of consciousness, such as early and acute psychosis, the temporal-lobe aura, dreaming, hallucinogenic drug states and **the Strauss-Kahn syndrome.** There is evidence that a loss of top-down control over **limbic activity** in hierarchically lower systems is equivalent to a **loss of the ego's control** over conscious process. **Failure** of system to **minimize free-energy** (suppress endogenous excitation) results in **disturbed affect, cognition** and **perception,** and this is seen in psychosis or in **Strauss-Kahn syndrome.**

Aggression as psychological stress

In this our study evident that **social conflicts** including **interpersonal difficulties** can also have **detrimental influences** on health. **Chronic conflictual interactions** foster **low-grade systemic inflammation** contributes to evolution of psychiatric, infectious, metabolic and **cancer**. [5,26,9,21] Our study associates with growing evidence about **mechanisms** converting **aggression stress** into **cellular dysfunction.** It is widely accepted that **psychological stress** affects the immune response, and repeated exposure to a stressor is immunosuppressive. Suppression of immunity is due to anti-inflammatory effects of adrenal glucocorticoid (GC) hormones. Ligation of GC receptors on mononuclear cells suppresses the expression of cytokines, chemokines, and adhesion molecules through a negative regulation of NFκB activation and function. **Psychological stress** and exposure to the stressor **social disruption (SDR)** increase cytokine production by monocytes/macrophages and reduce their sensitivity to corticosterone. Splenic monocytes/macrophages from socially stressed mice are primed to be more physiologically active than nonstressed controls. **Psychological stress** is not always immunospuppressive, if the stressor induces a state of functional GC resistance (for example the murine SDR causes resistance of splenic macrophages). [3] Repeated **social defeat** during SDR resulted in a significant increase in spleen mass and the number of splenic monocytes/macrophages and granulocytes. It indicates that repeated **social defeat** during the SDR stressor enhances innate immunity to *E. coli* infection and SDR significantly impacts splenic monocytes/macrophages. Several studies demonstrating that macrophages are primed

during repeated **social defeat.** In the nucleus, the translocated GC receptors acts as a ligand-dependent transcription factor to modulate the expression of **GC-responsive genes,** or to suppress activity of other transcription factors, like NF κB.

Strategy of authoritarian Hawks

In evolutionary terms different organisms adopt different behavioral strategies to cope with stress. For our conceptual framework of the **aggression stress** is central the strategy of **authoritarian Hawks,** showing that inefficient management of allostasis mediators may lead to violent behavior, development of impulse control disorders and **inflammation.**[19] In a competitive situation the Hawk shows **aggressive** behavior, stopping only if **injured** or when the opponent **submits.** The Hawk generally wins the entire resources. If the Hawk is unsuccessful, may have lower fitness because of energy loss, wounds, blood loss and infection, which can lead to **the inflammation**. This can be also a consequence for **the victims** of the aggression stress.[1,6] Authoritarian Hawks show a fight-flight response during which **an activation** of the hypothalamic-pituitary-gonadal **(HPG)** axis is increasing the plasma level of **the testosterone.** Testosterone **increases the likelihood of aggression** by stimulating **vasopressin** synthesis. Higher impulsivity may be a consequence of lowered activity of the tonic **5-HT** neurotrasmitter system.[24,26,14] Authoritarian Hawks with their high sympathetic reactivity are **more vulnerable** to developing tachyarhytmias than Doves. Shift of autonomic balance toward **sympathetic dominance** makes Hawks vulnerable to **sudden death** once apoptosis has developed in the heart. Sympathetic system hyperactivity affects not only the cardiovascular system but also **the immune system.** A growing number of animal findings strongly suggest that a hyporeactive HPA axis may be **pathologically significant** through a shift to **Th1 cytokines** that **increases susceptibility** to **chronic inflammation.**[17] Hawks have an increased risk of **wound**[12] and **infections** because they are more **aggressive** and **bolder** than Doves. **Th1** dominated cellular immune response in Hawks is very adaptive against infections. But this hyperimmune state together with a blunted HPA axis activity incures **costs** such as **the risk of inflammation** and **autoimmune disease.** The lower parasympathetic reactivity of Hawks show that they are less well equipped to inhibit the release of **macrophage cytokines** via **the vagal** parasympathetic route. The increased release of cytokines can contribute to **the costs of allostatic load.**[14]

NF-κB and Stat3 integrate interpersonal stress signals

Nuclear factor-κB (NF-κB) and Stat3 proteins are transcriptional factors,[28,13,25] which **integrate stress signals** and **orchestrate immune responses** also linked to **carcinogenesis. Cancer** development include: self-sufficiency in growth signals, insensitivity to growth inhibitors, evasion of apoptosis, limitless replicative potential, tissue invasion, metastasis and sustained angiogenesis. NF-κB signaling is involved in all these hallmarks. Recent experimental studies showing **the mechanistic pathways** by which NF-κB signaling contributes to **carcinogenesis. Inflammation promotes carcinogenesis,** NF-κB and Stat3 signaling integrate **interpersonal stress** signals during this process.[19,7,15] NF-κB and Stat3 **control** the expression of anti-apoptotic, pro-proliferative and immune response **genes.** These genes **overlap** and show **transcriptional cooperation** and **inhibition** between the two factors. Activation and interaction between NF-κB and Stat3 plays a key role in control of **the dialog** between **the malignant** cell and its **microenvironment,** with **inflammatory**/immune cells that infiltrate **tumors**.[2,12] Cytokines induced in response to NF-κB in immune cells of the tumor microenvironment lead to Stat3 **activation** in **both** malignant and immune cells. Within malignant and pre-malignant cells **Stat3 activates oncogenic** functions, within inflammatory cells it may also **suppress** tumor promotion

through its anti-inflammatory effects. **An unstable hierarchy** produces robust changes in allostatic state depending on the social status of the primates.[16] A relationship exists between **stress-related diseases** and one's behavioral strategy. It was observed that humans with type A personality are more aggressive and hostile, **extremely competitive,** impatient and always in a hurry. **Authoritarian personality type A** closely resembles the Hawk type.

Conclusions

Psychoneuroimmune interactions could be one of **the biologic mechanism** underlying correlations between **psychologic factors** and **cancer.** A possible **mechanism** suggested by recent studies are factors secreted by **leucocytes (cytokines)** which can influence both immune and CNS processes. The evidence for **physiologic pathways linking** the CNS and the immune system suggests that "hardwiring" is in place for regulation of the immune system by the CNS. The association between times of psychologic distress (aggression) and reductions in proliferative response of **lymphocytes** cultured with mitogens, are mitogens that activate **T-cells.** This *in vitro* measure of lymphocytes activation, sensitive to psychosocial influences is **linked** to any disease outcome. There are studies that have explored **the relationships** between **psychosocial variables** and natural killer **(NK) cell** activity. This studies support **the link** between **psychosocial factors (aggression)** and **alterations** in **immune function.**

Psychosocial influences on immune function providing a **biologic mechanism** that account for reported association between **psychosocial factors** and **cancer.** Three general categories of psychosocial variables appear to be related to cancer: **history** of psychologic distress (aggression), **social support,** and **personality variables.** The determination of **causal links** between psychosocial factors and the incidence of cancer is obscured by the long delay between **the initiation of malignancy** and **the detection of neoplastic disease. Tumors** can be induced by a number of different **mechanisms,** including **DNA tumor viruses, retrovirus** insertion near a cellular **oncogene,** and cellular **oncogene activation** occurring spontaneously or as a result of **carcinogen exposure.** There is evidence that the immune system can enhance the growth of some tumors as well as inhibit it. In the light of the independent evidence for a **relationship** between psychosocial factors and cancer, the evidence that the immune system plays a role in **cancer** raises the possibility that **psychoneuroimmune interactions** may play a role in **cancer.**

In conclusion, the research related to possible psychoneuroimmunologic processes in cancer provides support for the following hypotheses: (1) the outcome of some **cancers** can be influenced by **psychosocial factors,** (2) the activities of the immune system can influence the outcome of some **cancers,** (3) immune responses such **NK-cell** activity play role in defenses against **cancer**, appears be influenced by **psychosocial factors (aggression)**. Alterations in **immune defenses** can be investigated as a possible **mechanism** by which **psychosocial factors** could influence **cancer.** Chronic inflammation **promotes tumor** development and is not the one response but instead represents a dynamic, continuously changing **microenvironmental** process with various effects at subsequent stages of **tumorigenesis.** Multiple factors in both the host and the malignant cells, **the malignancy** has impact on **the inflammatory response** and vice versa.[14] Once the locus coeruleus (LC) become **hyperactive** due a positive correlation between hypercortisolism and increased cerebrospinalfluid (norepinephrine - NE), this core system may enter a vicious circle, because **the LC** can **inhibit the prefrontal cortex.** The allostatic load may be in their microenvironment **pathologically significant** through a **shift to Th1 cytokines** and increasing susceptibility to **chronic inflammation,** which can on the long term trigger various forms of **cancer** in humans**.**

Most of **tumors** contain inflammatory and immune cells macrophages and **lymphocytes,** which produce **cytokines** and other factors that promote **tumor** growth and survival. Tumor-promoting role of **immune** cells is manifested in **inflammation**-associated **cancers,** where tumors arise and grow at sites of **chronic inflammation.**[10] **Lymphocytes, IL-6, NF κ B** may be part of **the translational entry points** into the neural circuit regulating immune changes induced by **environmental stress,** leading to development of **cancer.**[11] The stressor significantly increased circulating levels of **IL-6** and **MCP-1,** significantly correlated with stressor-induced changes to three bacterial genera: *Cprococcus, Pseudobutyrivibrio,* and *Dorea.*[3,4]

Social conflicts caused by **the interpersonal aggression** mediated by **authoritarian type A personality** of males is involving complicated **immune network** of **the psychosocial** threat of **cancer** as **the end stage of inflammation.** It has been shown in a population of mice, that males with **high testosterone outnumbered** those with lower levels, but the presence of **too many aggressive** individuals resulted in a **crisis of the population.** This extends into humans a large corpus of animal research, suggesting that **an organism's physiology** is intimately regulated by **the interpersonal context** in which s/he resides. Due to the latest connotations we propose this personality phenomenon label as **"the Strauss-Kahn syndrome".**

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