Integrating the homeostatic imbalance

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1. Introduction and concept

> Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant. . . . It is the same thing which makes us mad or delirious, inspires us with dread and fear, whether by night or by day, brings sleeplessness, inopportune mistakes, aimless anxieties, absent-mindedness, and acts that are contrary to habit…..
>
> Attributed to Hippocrates; Fifth Century, B.C.

1.1. A Vulnerability That is More than Skin Deep

The Metmetian archipelago was founded in the year 2293 AD by a group of people who could not cope with the fast pace of the world at that time. For generations, there has been a string of severe psychiatric and physiological conditions haunting their blood lines and although the various nations they live in fairly succeeded in adopting strategies to cure these highly vulnerable people of their ills, the frequency of relapse and the status of constantly being at risk became virtually unbearable. The idea of moving away to start a settlement of the vulnerable was born during a group meeting of an advocate group for individuals suffering from psychiatric and other related disorders.

One very emotionally labile lady called Jexina, who was later recognized as the first Metmetian, had been suffering from emotional disorders all her adult life. She expressed her sorrow during one of the meetings and pondered as to how her life would have been better if she would be living on an island that is free from all the hassles of modern life. Every one in the gathering instantly recognized her thoughts and consensus was easily attained, among all those present, that this might be the only way for them to survive the world as it is. This led to the idea of moving to an uninhabited island where the vulnerable ones that could not withstand stressful life events, could start an alternative community based on protecting the people from environmental pathogens that led to series of disorders. These include both psychiatric and physiological conditions such as major depression, anxiety disorders, psychotic symptoms, gastrointestinal disorders, cardiovascular disorders, and a series of pain related disorders that had haunted these individuals for generations.

When the disease burden of the world became unbearable, suicide rampant among the youth, and there was no turning back to a slower pace of life, a slow but

steady exodus to a southern island called Hetzygon took place and the Metmetian archipelago was born.

The Metmetians lend their name from an inherited genetic trait. They carry more than seventy percent of the low activity variants of the major neuromodulatory enzymes. This allelic variation in their genes results in a reduced activity of enzymes such as catechol-O-methyltransferase (*COMT*) and brain derived neurotropic factor (*BDNF*). *COMT* plays a role in the degradation of catecholamines such as dopamine (DA) and norepinephrine (NA) with the *met* allelic variation of the functional polymorphism of the *COMT* genotype leading to a three to fourfold reduction in this degradation process. In the case of *BDNF*, this neurotropic factor is implicated in intracellular trafficking and activity dependent *BDNF* release, with the *met* allelic variation leading to a marked reduction of this process. Additionally, low activity allelic variations for the glucocorticoid, glutamtergic, gamma-aminobutyric acid (*GABA*), and monoaminergic neuromodulators, which were later called *met* alleles as in *COMT* and *BDNF*, were frequent in Metmetians. This genetic condition that is passed onto future Metmetian generations is the result of a rare mutation that led to a general inability of the body to produce enzymes responsible for the breakup of a broad class of the above named neuromodulators in the central and peripheral nervous system classified as G^3M^2B. These substances are neurotransmitters, hormones, biogenic amines, or neurotropic factors that make up the G^3M^2B subclass of neuromodulators. They are very functional in the maintenance of homeostasis and facilitate the central and peripheral response to cognitive, emotional and physiological processing necessary for the organism's adaptation to the ever changing environment.

A rare combination of these low catabolic activity allelic variations of the major neuromodulators led to the genetic trait that later became to be known as the Metmetian genetic condition. As a consequence of this reduced catabolic activity in their neuromodulatory system, Metmetians have an increased availability of catecholamines, glucocorticoids, *BDNF* and other stress-related markers in their brain/body which makes them especially vulnerable for stress related disorders.

The fact that the mammalian physiology has evolved such that adaptive mechanisms can in themselves become maladaptive and lead to disorders of severe etiologies in the face of persistent adverse circumstances, is rather unfortunate for the Metmetians. Given their genetic vulnerability to a variety of diseases triggered by environmental pathogens such as stressful experiences, their idea was that moving to an island where life could be adjusted such that even the most vulnerable individuals could prosper without a significant risk for developing stress-related diseases.

At the peak of Metmetian harmony, when fatalities or severe health conditions as a result of stressful life experience were reduced to zero, disaster struck hard at the heart of their social fabrics. Without warning of any kind, an extremely fast rolling object that was later identified as a huge boulder, the size of a foot ball field, broke off the southern cliff of mount Hetza and rolled down towards the sea, destroying everything in its path, including the sports complex with a huge boom. Pandemonium broke out, the survivors were in panic and people started running towards the open shores with hundreds venturing into the violet sea, desperate for a safer abode. The destruction was huge; the loss devastating; the whole sports complex and most of the surrounding buildings and virtually anything in the path of the giant rock was crushed. Bodies could be seen jumbled up amongst the debris. Remarkably however, a lot of the dead bodies were of those who died not directly due to the explosion but rather, as a result of a mysterious after effect they must have suffered. Bodies were scattered along the pavements that marked the flight path of survivors of the impact.

The damage was so immense that no emergency service no matter how organized and well equipped, could have handled the situation and taken care of the needs of the victims adequately. Most of all, the Metmetians were ill prepared for such a calamity. Their society was organized such that all difficulties which potentially could be experienced as stressful were avoided. One could imagine that the number of deaths that was directly caused by the disaster on the Metmetian Island of Hetzygon may just be the tip of the iceberg. One month after the disaster, a string of individuals began to develop sleeping disorders, and in a short time, half the youth were either suffering from major depression or other related disorders, or were affected by some form of somatic disorder like chronic pain or cardiovascular diseases. It became common place to see one person suddenly bursting out loud in cries which is most certainly echoed by others, for Metmetians are very well known for their highly empathic nature.

People began to report a multitude of complaints some of which were so complex that the physicians together with Metmetian thinkers and researchers were left dumfounded as to how to deal with the situation. The prevalence of emotional disorders like generalized anxiety, major depression (MD), post traumatic stress disorder (PTSD), and psychotic symptoms rose from near zero marks to about forty eight percent of individuals in the general population. Suicide, that was never heard of for years, became the number one cause of death and about seventy percent of the youth were addicted to at least one form of psychoactive drug or alcohol. Thus, the long term consequences of such a disaster became indeed apparent in Hetzygon.

The highly efficient dietary system that succeeded in maintaining health and prevents disease was not effective any more. The successful philosophy of prevention became rather useless when psychiatric disorders with somatic symptoms reached pandemic proportions. The strain of events that followed the disaster impacted the Metmetian society enormously. Even the preservation of law and order that every one took for granted, crumbled away when some highly emotional youngsters started indulging themselves in behaviors that were far from being acceptable.

This unfortunate turn of events was later commented on by one of the Metmetian physiologists as a reminder of the outdated hypothesis in psychoneuroendocrinology, also known as the *stress diathesis theory*. As he put it in an emergency conference designed to find solutions to the crisis: our present crisis is a resonance of the *stress diathesis theory*. According to this theory, appropriate responsiveness to daily life stressors is crucial for adequate functioning, while inappropriate responsiveness impair growth and lead to a number of physiological and psychiatric disorders (Plotsky 1998; McEwen 1998; Sapolsky 2000; Chamandari et al. 2005; Moffitt et al. 2005).

The history of the Metmetians was strongly influenced by their existing genetic risk. This was the strongest motivating factor behind the creation of a near stress free archipelago. However, unpredictable disasters such as these leading to the prevalence of emotional disorders at pandemic proportions underscore the complex nature of gene-environment interaction in the maintenance of health. Thus the Metmetian tragedy and the turn of events that led to it, epitomizes that some vulnerabilities are simply more than skin deep. Such vulnerabilities, that are strong determinants of a large proportion of the disease burden facing the world today, warrants careful and meticulous scientific investigations, as suggested in Figure 1.1 below.

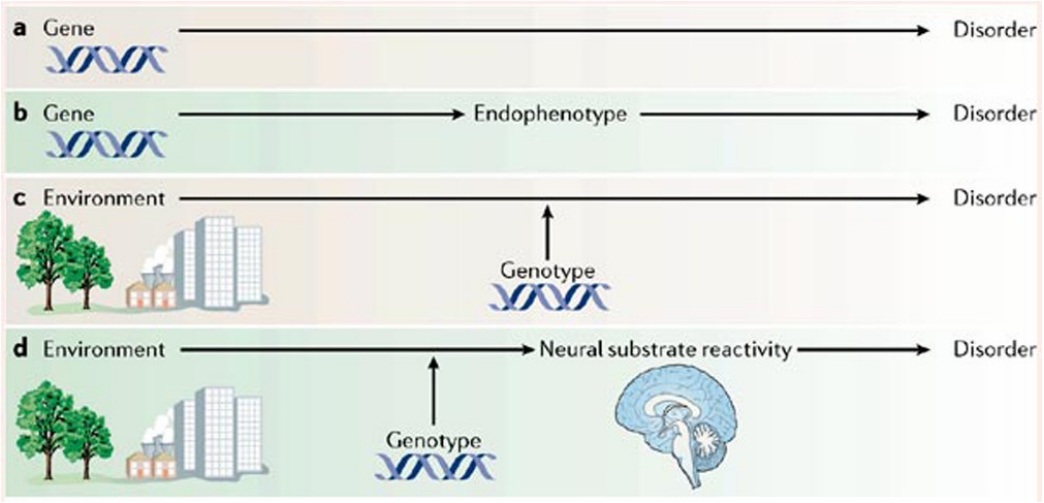

Figure 1.1. Adopted from Caspi and Moffitt 2006. Approaches to psychiatric genetic research. (a) The gene-to-disorder approach assumes a direct linear relationship between genes and disorder. (b) The endophenotypes approach replaces the disorder outcomes with intermediate phenotypes. (c) The gene-environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. (d) Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene-environment interaction.

1.1.1. Fusion of Mind and Body

Modern day reality however, is far from being Metmetian. While the Metmetians are unique in their enormous homogeneity relating to their genetic risk factors, present day humans tend to be diverse in their genetic susceptibility to stress related disorders. A bulk of the Metmetians suffered the unbearable consequence of the fateful disaster; however, it is likely that similar effects will be evident in not more than 20 percent of any typical human population in the year 2006, given a similar disaster. This implies that unlike the Metmetian population, there exists a normal distribution within a given human population as to how prone individuals are to the consequences of life stress. Regardless, the disease burden in industrial economies of present times is strongly impacted by a prevalence of stress related psychiatric disorders like MD, that are believed to have genetic origins (Caspi and Moffitt 2006; Meyer-Lindenbergh and Weinberger 2006).

The human body has evolved to react to the outside world through a cascade of mechanisms. Stressors that are of evolutionary importance, like predator encounters, leads to a cascade of bodily responses. These physiological mechanisms in conjunction with cognitive processes are necessary for adaptation and survival. However, given the individual differences in the bodily responses to environmental challenges, these biologically determined factors that to some extent mediates personality, may perhaps also modulate disease vulnerability to complex diseases like MD. Co-occurring psychiatric disorders could therefore be seen as an ‘extreme’ of interindividual difference in coping to stressful experience. Indeed, in some people, stress and extreme emotional encounters leads to coping and successful adaptation, while in other, similar experiences can lead to severe health consequences, and in worst cases death.

Present day reality that is continuously recruiting our abilities to adapt to either desirable or adverse changes in our environment. This process of environmental adaptation goes hand in hand with internal bodily changes in the form of autonomic arousal. Similar to avoiding burns or extremely heated environments, fighting off hard and fierce an attack of a disorientated rascal on the streets, running away from a

menacing predator, or avoiding psychologically stressful or emotional conditions, the human body undergoes physiological changes that are designed to maintain balance (homeostasis) during the experience of daily stressors like a job interview. Unlike evolutionarily valid stressors such as predator encounter, modern day stressors like job interviews are social rather than physical in nature. Similar to these very somatic examples like a predator encounter, humans undergo internal bodily changes consciously or unconsciously during exposure to socially emotional and stressful experiences. The physiological responses that accompany these experiences enable us to maintain the integrity of our body and thereby enhance survival in challenging situations. Such actions of either avoidance or approach in situations where the environmental events are favorable or threatening to our psychological and physiological well being, are designed to maintain the balance of our inner milieu as well as our needs and goals.

As Claude Bernard, the nineteenth century French physiologist, was intrigued by the seemingly trivial distinction between an animal's external environment and its internal environment, he was struck by the *non*trivial fact that while the external environment can fluctuate considerably, an animal's *internal* condition is kept relatively constant. For example, the human body temperature remains about 37º C, and a mere five degrees difference leads to death (Churchland 2002). Homeostasis—maintenance of biological values within narrowly defined range—is a buffer against environmental fluctuations. This way, organisms are in constant interaction with their environment and are homeodynamic rather than homeostatic (Rose 2001). As Patricia Churchland puts it; "the brain keeps track of levels of blood sugar, oxygen, and carbon dioxide, as well as blood pressure, heart rate, and body temperature, in order to detect perturbations to the internal milieu that are detrimental to the animal's health." Deviation from the normal set points cause an orchestrated set of neuronal responses that ultimately cause the animal to seek either food, water, warmth, a hiding place, or the like, thereby restoring deviant values to their normal values.

By homeostasis, we are referring to the term of "being in balance" and whatever knocks homeostasis out of balance causes stress and is eventually emotionally appraised as negative or positive (Sapolsky 2000). Homeostatic functions—and, in particular, the ability to switch between the different internal configurations for *flight* and *fight* from that needed for *rest* and *digest*—require coordinated control of heart, lungs, viscera, liver, and adrenal medulla in a set of interconnected structures, with the brain stem being anatomically important in coordinating this process (Damasio 1999).

The maintenance of an internal milieu requires the setting of a dynamic range enabling the brain to know when an organism is being threatened. Thermal pain therefore, should be coordinated with withdrawal, not approach, cold-temperature with shelter seeking, not with sleeping and very hostile environmental conditions with fear and flight and not with approach-behavior (Churchland 2002). These above mentioned behavioral repertoires are directly under the influence of brain mechanisms that enables our ability to assign value to surrounding events and directs our choices.

By the same token, emotions can therefore be seen as the brain's way of making us do and pay attention to certain things. Like in the face of a severely threatening situation, say an approaching predator, our bodies are programmed such that flight away from the predator will be the most logical option. Thus, sensory feelings of emotions evolved in response to those environmental events that have consistently presented opportunities or threats to biological survival in ancestral environments. That is, emotions are assignments of value that direct us one way rather than another,

and they seem to have a role in every aspect of self-representation, and certainly in body representation (Churchland 2002). A typical example is the choice of running away from any bodily source of harm instead of approaching. In physiological terms, brief periods of oxygen deprivation give rise to overwhelming feelings of needing air; extreme hunger and thirst can make us feel so desperate as to banish all thoughts of anything but water and food. Satisfaction is felt after feeding, sex, and successful predator avoidance. More generally, self-representation is underpinned by powerful feelings (MacLean 1949; Damasio 1999).

1.2. But Where Lies The Roots to Feelings?

> "PLEASURE, ELATION, EUPHORIA,
> ecstasy, sadness, despondency, depression,
> fear, anxiety, anger, hostility, and calm—these
> and other emotions color our lives. They
> contribute to the richness of our experiences
> and imbue our actions with passion and character."
>
> Iverson, Kupferman and Kandel 2000.

States of bodily excitement distinguish "passion" from "cold reason" (Critchley 2005). Everyone is familiar with the phenomenon of shivering with fear, flushing with anger or embarrassment, and quickening of heart during anxiety or love. These bodily states represent the peripheral components of subjective emotional experience, with a hierarchy of homeostatic mechanisms being responsible for regulating functions within and across bodily systems (Critchley 2005). As humans, we perceive feelings from our bodies that relate to our state of well-being, our energy and stress levels, our mood and disposition (Craig 2002). At the organ level, coordinated control is mediated primarily by neural and humoral pathways, with the adaptive control of behaviour within the environment topping the hierarchy. In this sense, internal bodily changes could be seen as evolutionary adaptations that influence behavior, signaling physical needs such as hunger, but also preparatory bodily responses such as states of readiness evoked by threat, all shaped by experience and stored in memory to serve future behavior (Darwin, 1898).

The autonomic nervous system represents the principal regulatory route of internal bodily functions. Sympathetic and parasympathetic autonomic axes provide neural input into every major bodily system (Brading, 1990). Their interaction enables continuous control of "vegetative" processes and the dynamic modification of bodily states in response to environmental challenges. By dilating vessels of the musculature as a result of concomitant reduction of blood supply to the gut, sympathetic activities facilitate motor behavior and thereby increase cardiac output. These physiological activities facilitates the *fight* and *flight* behavior in times of danger. In contrast, parasympathetic activity promotes recuperative functions effecting heart rate reduction, lowering of blood pressure, and slowing of gut motility, facilitating *rest* and *digest* related states. Bodily states of arousal associated with survival (e.g., fight and flight responses) are typically characterized by increased sympathetic activity and, usually, decreased parasympathetic activity (Cannon, 1929; Porges, 1995; Morrison, 2001). Thus subsets of autonomic arousal responses that affect visible visceral regions have developed into potent social cues that can betray an individual's motivational state (Darwin, 1898; Ekman et al. 1983).

1.2.1 Stress and the Emotions

In conjunction with the feelings of emotions, exposure to hostile conditions initiates responses organized to enhance the probability of survival. Such adaptations, known as the stress response, consist in a variety of changes in behavior, autonomic and neuroendocrine function, leading to release of different hormones. The activation of the hypothalamic-pituitary adrenocortical (HPA) axis, in concert with epinephrine and norepinephrine from the sympathetic nervous system and adrenal medulla, plays a pivotal role in the stress response. Stress initiates a cascade of events in the brain and peripheral systems that enable organisms to cope with and adapt to new and challenging situations. For this reason, the physiological and behavioral responses to stress are generally considered to be adaptive reactions. However, when stress is maintained for long periods of time, most physiological systems are negatively affected because of the prolonged exposure of target cells to physiological stress mediators (McEwen 2002).

Physical stressors include temperature, pain, itch, muscular and visceral sensations. Sir Charles Sherington conceptualized a sense of 'the material me' by considering that all of these feelings are related and form a foundation of the sense of one's physical self (Sherington 1900). Sherington later codified the senses into teloreceptive (vision and hearing), exteroceptive (touch), chemoreceptive (smell and taste), proprioceptive (limb position) and interoceptive (visceral) modalities, and categorized temperature and pain as aspects of touch (Sherington 1948). Recent findings on the functional anatomy of lamina 1 spinothalamocortical system indicate that interoception should be redefined as sense of the physiological condition of the entire body and not just the viscera (Craig 2002; Craig et al.. 2000). This system is believed to be a homeostatic afferent pathway that conveys signals from small-diameter primary afferents that represent the physiological status of all tissues of the body (Craig 2002). However, it is only now that the fundamental recognition of pain, temperature and other bodily sensations as interoceptive, rather than exteroceptive is beginning to emerge (Craig 2002; Critchley 2005).

A key feature that is common to pain, temperature and other bodily feelings like sensual touch is their inherent association with emotion (Craig 2002). These feelings have not only sensory, but also affective and motivational aspects. Physiological stressors like pain, temperature and touch, all generate inseparable affect (pleasantness or unpleasantness) representative of the physiological condition of the body that are directly related to homeostatic needs and associated with behavioral motivations that are crucial for the maintenance of body integrity, with their neural representations reflecting this homeostatic primacy (Craig 2002). Interestingly, these seemingly different sensations are represented to some extent by a common brain network, suggesting that even if there may exist different subcomponents of homeostasis, certain brain regions such as the insula and cingulate cortices, may be involved in the regulation of mechanisms relevant for general homeostatic maintenance (Craig 2002).

Recent neuroimaging studies have greatly enriched our understanding of the neuroanatomical substrates underlying perception, cognition and emotion (Wang et al. 2005). Data on the processing of different emotions suggest a common neural network involving the prefrontal cortex, anterior cingulate, amygdala, insula, basal ganglia (Davidson and Irwin 1999; Dolan 2002). The neural correlates of vigilance and sustained attention have been largely localized to the right prefrontal and parietal lobes and the thalamus (Sarter et al. 2001). The right prefrontal cortex may play a key

role in the brain's response to stress, because this brain area is a primary part of both the emotion and vigilance network (Wang et al. 2005). Moreover, animal and human studies have demonstrated descending influences from prefrontal and limbic cortices (cingulate, medial temporal. and insula) and amygdala on autonomic control mediated by hypothalamic and brainstem centers (Pool and Ransohoff, 1949; Kaada, 1951; Gelsema et al. 1989; Neafsey, 1990; Fish et al. 1993; Oppenheimer et al. 1992; Mangina and Buezeron-Mangina, 1996; Asahina et al. 2003; Critchley 2005). Most importantly, neurons that are either the target or the releasing site of an array of stress mediators (neurotransmitters and hormones such as corticotrophin releasing hormone 'CRH') have been identified in the amygdala and cingulate areas (Charney 2004; Carrasco et al. 2003; Craig 2002).

Where autonomic arousal occurs in anticipation of behavioral responses, feedback of bodily changes reinforces stimulus processing to influence behavioral judgments, implicitly or explicitly (Damasio et al. 1991; Damasio, 1994; Bechara et al. 1997). Central representation of these internal motivational signals is hypothesized as the origin of emotional feeling states (Lange, 1885; James 1894; Damasio 1994, 1999). Furthermore, William James argued that the feelings from our bodies are the basis of self awareness and emotion (James 1890). As James wrote in the *Principles of Psychology*; "our natural way of thinking about these coarser emotions is that the mental perception of some fact excites the mental affection called the emotion, and that this latter state of mind gives rise to the bodily expression." According to his theory he noted that *the bodily changes follow directly the perception of the exciting fact, and that our feeling of the same changes as they occur* IS *the emotion* (James 1890). James went on to urge the vital point of his theory: *If we fancy some strong emotion, and then try to abstract from our consciousness of it all the feelings of its bodily symptoms, we find we have nothing left behind*, no 'mind-stuff' out of which the emotion can be constituted, and that a cold and neutral state of intellectual perception is all that remains (James 1890).

Notably, the absences of this direct interoceptive representation in sub-primates imply that they cannot experience feelings from the body in the same way that humans do (Craig 2002). In humans, lesions of the dorsal insula interrupt these feelings (Schmahmann & Leifer 1992; Greenspan & Winfield 1992), disrupts homeostatic processing (Craig 2002) and cause permanent loss of discriminative thermal sensation. Several studies in the domain of pain, interoceptive awareness of the body, but also studies employing positively valenced stimuli like pleasant music, sensual touch and sexually arousing stimuli, have often implicated the anterior insula/frontal opercular cortex (Craig 2002) (see Figure 1.2). Such functions enable structures like the insula to code the physiological correlates of the body's needs (Cabenac 1972; Mower 1976). As Craig puts it; compare the pleasant feeling of cool water when your body is overheated with gnawing discomfort generated by the very same cool stimulus when you are 'chilled to the bone'. Thermoregulation is therefore a primal evolutionary requirement for all animals, particularly homeothermic mammals, and the affective aspects of such feelings correspond to the motivations that are essential for behavioral thermoregulation and homeostasis—that is survival (Satinoff 1978; Blatteis 1998). These cortical regions constitute a primary interoceptive image of homeostatic afferents that codes distinct sensations including temperature, pain, itch, muscular and visceral sensations, sensual touch, but also experiences of stress and emotions that are related to feelings from the body (Craig 2002) (see Figure 1.2).

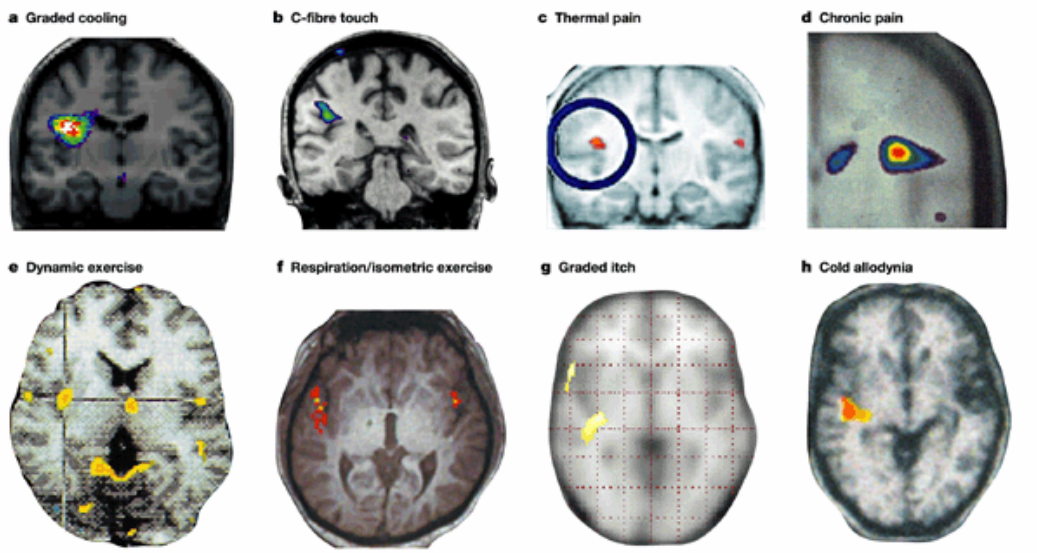

Figure 1.2. Adopted from Craig 2002. This figure shows that several experiences ranging from (a) graded cooling, (b) sensual touch, (c) heat pain, (d) chronic pain, (e and f) exercise, (g) itch, and (h) cold experience all recruit the anterior insula/frontal opercular cortex. As noted earlier in the text, a common feature of these stimuli is their strong relationship to bodily feeling states. A consistent activation of the insular cortex in all these feeling states regardless of modality and valence implicates this region to be involved in the regulation of bodily feeling states and thereby ascribes this region a pivotal role in the maintenance of homeostasis.

1.2.2. Embodied Feelings

A rather intriguing illustration of how emotional feelings are not so strongly distinguishable from bodily feelings is the following. An individual who went amok and attempted to carry out a mass murder in a market place on the edges of a populous city in sub-Saharan Africa was overpowered and tied down. He started a desperate lamentation in the Malinke language, screaming: **"**I have this strong feeling of failing myself and all my people and do not wish to live any longer because the *crawling of extreme sadness in my spine* became simply unbearable. Although the fear of killing myself has strongly *stiffened my marrows*, the idea keeps coming to my mind that if I kill a few people, this fear may wane and as a result, I may even feel a bit of *happiness warming up my glands* which may give me courage to shoot myself *cold*. Yesterday, I felt enough *strength in my fibers* and had decided to go some place and kill as many people as possible, a place where I have no *bodily affecting individuals*. After loading my assault rifle, I walked the whole night till I got here this morning. I chose the moment when I saw that enough people were around at a closer range and started shooting straight out. But then during the shooting, I saw the one *who usually stresses up my heart* in my line of firing and *my body died* in an instant, and that was when you guys took hold of me."

What the poor fellow was trying to convey was a highly tragic story full of bodily emotional experiences or anticipation of these experiences. Sadness crawls in his spine; fear stiffens his marrows; happiness warms his glands. But most profoundly, he calls his relatives and loved ones as those that affects his bodily responses; and indeed after seeing the lady who usually stresses up his heart in his line of firing (referring to someone he is desperately in love with), his body simply died of sympathy for that individual. This story demonstrates some intriguing qualities of the Malinke language. It shows that speakers of such a tongue do indeed inevitably see emotional feelings as abstract as being in love or sympathizing with someone as strongly embedded in bodily feelings. Even though these people are not advanced in the study of human physiology as far as the modern western scientific methods are

concerned, their language is such that they recognize the importance of bodily changes in the generation of emotions.

If we step from the southern lamentation and examine an even more elaborate manifestation of grief as described by a nineteen century Danish physiologist, C. Lange, here is a summarized version his embodied account of grief: "The chief feature in the physiognomy of grief is perhaps its paralyzing effect on the voluntary movements. This effect is by no means as extreme as that which fright produces, being seldom more than that degree of weakening which makes it cost an effort to perform actions usually done with ease. It is, in other words, a feeling of weariness; and (as in all weariness) movements are made slowly, heavily, without strength, unwillingly, and with exertion, and are limited to the fewest possible. By this, the grieving person gets his outward stamp: he walks slowly, unsteadily, dragging his feet and hanging arms. His voice is weak and without resonance, in consequence of the feeble activity of the muscles of expiration and of the larynx. The tonicity or 'latent innervations' of the muscles is strikingly diminished. The neck is bent, the head hangs ('bowed down' with grief), the relaxation of the cheek- and jaw-muscles makes the face look long and narrow, the jaw may even hang open. And what is not obvious to the eye is that the mouth grows dry, the tongue is sticky, and a bitter taste ensues which, it would appear, is only a consequence of the tongue's dryness. The expression 'bitter sorrow' may possibly arise from this. There is one most regular manifestations of grief, which apparently contradicts these other physiological phenomena, and that is weeping, with its profuse secretion of tears, its swollen reddened face, red eyes, and augmented secretion from the nasal mucous membrane."

If we try to forget the depressing physiology of grief and delve into the exciting state of fear as Darwin wrote of its bodily effects: "Fear is often preceded by astonishment, and is so far akin to it, that both lead to the senses of sight and hearing being instantly aroused. In both cases the eyes and mouth are widely opened, and the eyebrows raised. The frightened man at first stands like a statue motionless and breathless, or crouches down as if instinctively to escape observation. The heart beats quickly and violently, so that it palpitates or knocks against the ribs; but it is very doubtful whether it then works more efficiently than usual, so as to send a greater supply of blood to all parts of the body; for the skin instantly becomes pale, as during insipient faintness. That the skin is much affected under the sense of great fear, we see in the marvelous manner in which perspiration immediately exudes from it. The hairs also on the skin stands erect; and the superficial muscles shiver. In connection with the disturbed action of the heart, the breathing is hurried. One of the best-marked symptoms is the trembling of all the muscles of the body; and this is often first seen in the lips. From this cause, and from the dryness of the mouth, the voice becomes husky or indistinct, or may altogether fail."

1.3. The Question at Hand

By now the reader might be reminded of the existing relationship between emotional and stressful experiences and bodily feeling states. The main purpose of the present thesis is to investigate the underlying physiological correlates of emotional and psychological stress response. We will address the bodily responses (in terms of the functional neuroanatomical correlates of emotional experience on the one hand, and peripheral hormonal responses to the experience of psychological stress on the other) to emotional and stressful experiences and their role in the maintenance of individual well being.

It is very important to recognize that the sensory system that codes for emotional, physiological as well as psychologically stressful experiences recruits part

of an entire physiological network involved in the maintenance of homeostasis (Wang et al. 2005). In line with this view, it has been proposed in the somatic marker hypothesis that the subjective process of feeling emotions requires the participation of brain regions that are involved in the mapping and/or regulation of our continuously changing internal states—that is, in homeostasis (Damasio 1993). These feelings help to guide behavioral decisions that affect survival and quality of life by producing a 'perceptual landscape' that represents the emotional significance of a particular stimulus that is being experienced, or of a projected future action by means of a further 'as-if-body loop' mechanism (Damasio et al. 2000). Evidence indicating the existence of a relationship between brain stem activity (a structure strongly implicated in homeostasis regulation) and subjective feelings comes from human imaging studies showing an interaction of feelings and emotions with many aspects of subconscious homeostatic processes. (Sawchenko et al. 1996; Craig et al. 2000; Damasio et al. 2000; Craig 2002).

Such a conceptualization of considering both the emotions and psychological stress as involving similar homeostatic processes of the body provides an easy formulation for somatization under emotional stress (i.e., perceiving both the stress and emotional experience as rooted in related bodily responses). Thus, the *chronic* homeostatic imbalance one undergoes after a traumatic event, (e.g., such stressful experience like surviving a terrorist attack in which some closely-related individuals lost their lives), may be similar to the *acute* homeostatic imbalance that might result from a near death escape from a fierce predator or traffic accident. Similarly, these considerations imply that several unexplained somatic/pain syndromes such as fybromyalgia, chronic pain, diabetes as well as psychosomatic disorders, could be related to homeostatic dysfunctions, rather than to tissue damage (Craig 2002). Support for such a concept stems from the theory that stress promotes adaptation ("allostasis"), whereas a perturbed diurnal rhythm or a failed shutoff of mediators after stress ("allostatic state") may in time, lead to wear and tear on the body ("allostatic load") (McEwen 1998; 2003). Thus, neural changes mirror the pattern seen in the cardiovascular, metabolic, and immune systems, that is, short-term adaptation versus long-term damage.

Allostatic load can therefore lead to impaired immunity, atherosclerosis, obesity, bone demineralization, and atrophy of nerve cells in brain. Allostatic load is seen in major depressive illness and may also be expressed in other chronic anxiety disorders such as post traumatic stress disorder (McEwen 2003). Thus allostasis depends on personality type and the associated stress response (Korte et al. 2005). According to this view, the benefits of allostasis and the costs of allostatic load, leads to different trade-offs in health and disease, thereby reinforcing a Darwinian concept of stress. *But how does the bodies' quest for the maintenance of homeostasis in the face of environmental challenges (i.e. stress and emotions) affect the brain?*

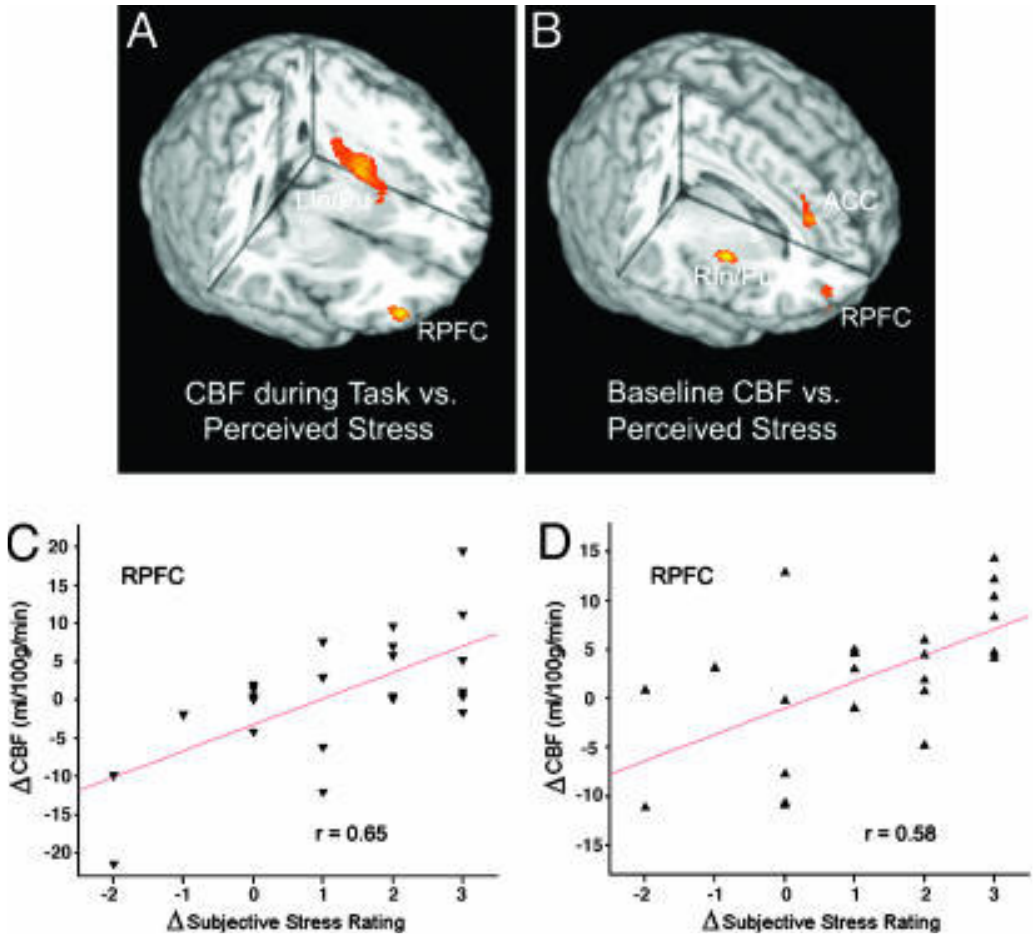

Figure 1.3. Adopted from Wang et al. 2005 PNAS. Three-dimensional rendering of the regression-analysis results, which use the CBF change during stress tasks (high-stress - low-stress task) (*A*) or the CBF change at baseline (baseline 2 - baseline 1) (*B*) as the dependent variable and the change in perceived stress from the low- to high-stress task as the predictor. Also shown are scatter plots of changes in CBF during stress tasks (*C*) and at baseline (*D*) as a function of changes in perceived stress between the two stress tasks. Each data point represents one subject. Mean CBF values are drawn from the ROI defined by the activation cluster. Right prefrontal cortex (RPFC) $x = 42$, $y = 54$, $z = -10$, 211 pixels, $Z = 3.59$ in *A*; $x = 32$, $y = 58$, $z = -2$, 118 pixels, $Z = 2.98$ in *B*. Anterior cingulate cortex (ACC) $x = 10$, $y = 38$, $z = 24$, 156 pixels, $Z = 3.22$; left insula/putamen $x = -32$, $y = -8$, $z = 4$, 811 pixels, $Z = 3.46$; right insula/putamen $x = 38$, $y = 2$, $z = 2$, 144 pixels, $Z = 3.73$.

1.3.1. Empirical Approach

In this thesis, individual differences in the perception and experience of social emotional interactions, psychologically stressful experiences, and genetic determinants of endocrine and subjective psychological stress response in low and high risk individuals will be examined. The cascade of peripheral endocrine response to psychological stress, coupled with the neural response to emotional experience could be seen as an organisms adaptation processes that have developed to serve short term purposes. In the long-term however, the result of this processes may be either adaptive or maladaptive depending on the nature of individual's genetic make-up and the severity of the environmental stressor (Plotsky et al., 1998). This is supported by the accumulating empirical evidence indicating that traumatic and stressful life-events are potential risk factors for the onset of certain psychiatric disorders (Brown and Harris 1978; Ormel et al. 2001).

In this vein, genetic determinants of the stress responses are believed to influence the degree of individual's vulnerability to stress-related emotional disorders (Caspi et al. 2003; Charney 2004). In *chapter 2* an experimental approach will be used to study the involvement of neural networks in the brain by inducing social emotions in healthy volunteers while undergoing functional magnetic resonance imaging (fMRI). The primary research question was to determine if the same brain areas that are implicated in the regulation of homeostasis as reported in studies examining the human stress response are recruited during the experience of these emotions. To these aims, we will induce the emotional states of happiness, sadness, and fear in individuals using film clips with emotional content as a sort of pilot study in which environmentally valid social emotional stimuli will be presented. The goal of this emotion-induction paradigm was to map the neural substrates commonly involved in the processing of all these emotions. Although not many studies have focused on the neural underpinnings of general emotional processing, identifying such areas may consolidate the idea of an existing biological substrate of homeostatic maintenance. This way, neural mechanisms underlying the arousal and bodily responses involved in emotional experiences, may not be specific for one emotion, but rather encompassing different emotions. Inducing emotions, however, is not an easy task in a laboratory environment. However, gustatory emotions like disgust and food related pleasure (hereafter called food-emotions, where with food, we mean both liquid and solid nutrients) are particularly well suited for scientific investigation in humans. This is possible because unlike other basic emotions, they can be reliably and repeatedly triggered in ethically sound ways by presenting participants with pleasant or unpleasant olfactory or gustatory stimuli.

In *chapter 3*, we capitalized on this possibility and investigated the neural basis of our understanding of other individual's basic emotions relevant for feeding behavior. Using event related fMRI, we investigated if subject's empathy scores are predictive of the intensity of activations in their insula and other regions that do not discriminate between perception and experience of both food related disgust and pleasure.

Disgusting food substances always induce aversive emotional responses that can go as far as causing people to become sick (nausea) and eventually vomit because such bodily feelings may prevent food poisoning and enhance survival. Delicious food substances on the other hand, do in fact induce a pleasant emotional response that signal appetitive reward and enhance survival. What is common to both food related disgust and pleasure however, is the ability of both experiences in affecting the internal bodily states and thereby homeostasis.

In *chapter 4*, we will investigate effects of individual differences in the functional polymorphic variations of *COMT* (a monoaminergic gene involved in the metabolism of catecholamines) on subjective and endocrine responses to acute psychosocial stress in a laboratory paradigm. Linking behavioral and neuroendocrine responses to validated experimental stress paradigms may enable us to examine the role of genetic polymorphisms in determining differences in individual susceptibility to neuropsychiatric disorders. Thus, individuals with varying degrees of susceptibility to major depression will be included to enable us to delineate the role of *COMT* allelic variation in the human stress response, as well as the relationship between this genetic variable and the individual's degree of susceptibility to major depression in the face of stress. Establishing such a relationship will increase our understanding of the role of genes in the maintenance of homeostasis and psychological well being.

Interactions between genetic makeup as determined by individual's *COMT*, monoamine oxidase-A (*MAOA*) and serotonin transporter (*5-HTT*) allelic variations in terms of their physiological and subjective response to acute psychosocial stress will be examined in Chapter 5. Additionally, a similar complex genetic involvement in homeostatic maintenance will be studied during an endocrine challenge (Combine Dexamethason/CRH challenge) in the same chapter. This will enable the examination to genetic effects of hormonal regulation, in the absence of psychological stress.

To the best of our knowledge, this is the first time that the relationship has been studied between genetic polymorphisms and the behavioral and neuroendocrine response to an experimental stressor in both healthy volunteers, first degree relatives and patients with major depression. A finding of gene-gene interaction in endocrine response to environmentally challenging experiences will enable us to demonstrate the complex modulatory roles of genes in individuals' continuous quest for homeostatic maintenance, failure of which might lead to disease in the long run.

The attempt to investigate environmental experiences be they, psychologically stressful, or emotional in nature, is a key goal of this thesis. Integrating findings of brain responses to emotional induction and peripheral endocrine responses to the experience of stress with earlier findings of neural mechanisms underlying stress and emotional experience may enable us to suggest the existence of shared networks involved in the processing of stress and the emotions. Here, we will focus on the idea that stress and the emotions are linked by homeostasis. Key to understanding the biological basis of vulnerability to stress related disorders like MD may therefore be the understanding of normal and abnormal physiological mechanisms relating to the maintenance of homeostasis, in the face of environmental challenges. We will examine the individual differences in the cascade of physiological responses by examining how individual differences modulate brain reactions to other people's emotions. Second, we will study the influence of genetic makeup in peripheral endocrine and behavioral response to stressors.

Social emotional behaviour, like psychosocial stress, can be adaptive (e.g. understanding another individual) or maladaptive (e.g. Social Phobia). The examination of interactions between individual differences in genetic make up in relation to physiological responses to psychosocial stress, in conjunction with the neural mechanisms regulating empathy, may help bridge the gap between self and other homeostasis. Studying the individual difference in terms of both empathic tendency as well as genetic differences in physiological response to psychosocial stress, may enable us to make a small contribution in the understanding of social emotional behaviour relevant for mental health.

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