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REVIEW

An extended concept of altered self: Chronic fatigue and post-infection syndromes[☆]

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Summary

Sickness behavior in active infectious diseases is defined here as the responses to cytokines and other mediators of inflammation as well as the adaptability of a pre-existing integrated immunological, psychological, neurological, and philosophical self. These complex behaviors are biologically advantageous to the afflicted individual, but they also impact surrounding individuals. If chronic conditions, such as chronic fatigue syndrome or post-infection fatigue, exhibiting these behaviors follow infection in the absence of ongoing changes in immunological self associated with an active infection or subsequent injury, they are currently considered illness states rather than true diseases. Self-referential recognition (interoception) of bodily processes by the brain and subsequent unconscious and conscious adaptive responses arising in the brain, i.e., in the endocrine system and immune systems, which are initiated during the infection and would normally lead to positive maintenance, may become maladaptive and lead to an "extended altered self state." Exploratory measurements of such alterations using a "top-down" approach such as monitoring responses to appropriate challenges can be obtained using functional brain imaging techniques. Once identified, processes remediable to biological/pharmacologic and/or psychological intervention can be targeted in directed trials.

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1. Introduction

This hypothesis-generating essay addresses the questions: (1) Why do people feel sick during an infection? (2) Are there long term consequences of acute infection-related disease responses that require an expanded approach in considering pathophysiology of chronic illnesses? The essay addresses these questions based on the model of “altered self” as established in immune responses to infection, but extends it into a brain function model applicable to chronic illness syndromes in general and proposes testable hypotheses.

Acute infectious diseases are defined by the type of infectious agent, its target organs, and by the cellular and humoral immune responses that collectively lead to specific tissue injury and clinical consequences, such as cough in pneumonias and generalized signs such as fever. The sickness behavior complex accompanying these diseases, experienced as fatigue, malaise, irritability, disturbed sleep, and inability to concentrate, also results from activation of the immune response network (Hart, 1988; Dantzer, 2001; Vollmer-Conna et al., 2004). The individual’s life history, knowledge, and perception of illness contribute to sickness behavior (Imboden et al., 1959). Dantzer (2004) suggested a motivational component to its purposes, implying conscious or unconscious recognition of a baseline state from which referential actions are elicited.

2. Disease, illness, and sickness

Because of the divergent disciplines called upon in this essay, a discussion of the meanings of the words disease, illness, and sickness is necessary. The issue is compounded by the attribution of an altered state of health to all three terms. Comparison of the origins of the words “ill,” “sick,” “illness,” “sickness,” and “disease” shows their interdependency (Oxford English Dictionary, 2007). Several authors, for example, Twaddle and Nordenfelt (1994) and Hofmann (2002) attribute disease to “an organic phenomenon (physiologic event) independent of subjective experience and social convention.” Whereas illness is considered a subjective undesirable state of health or a feeling state referred to by expression of symptoms. Although only “somatic” conditions are included in the Hofmann, Twaddle, and Nordenfelt discourses, psychiatric conditions such as depression would qualify for the illness

label based on its definitional requirements, but as the biology of depression becomes clear, it will likely be considered a disease. In order to fulfill Twaddle’s definition of sickness (Twaddle and Nordenfelt, 1994), a societal recognition of a disease or illness that frees the individual from ordinary duties of work and makes him or her eligible for economic assistance is required. Hofmann (2002) suggests that the three constructs may occur in varying combinations. The first is illness and sickness in the absence of disease, such as low back pain; a construct on the surface that is germane to this essay. He also suggests that disease and illness may coexist in the absence of sickness, such as in the common cold or aging, because society does not accept a sick role for these individuals (perhaps it should). The third situation is disease and sickness in the absence of illness leading to physician intervention, such as in pre-clinical diabetes mellitus. Eisenberg (1977), writing from a medical rather than a sociological point of view, shares the concepts of a biological origin for disease and a subjective origin for illness.

3. Sickness behavior

The term “sickness behavior” appears in two divergent contexts in the 20th century. It appears to have been introduced in evaluation of the sick role or illness behavior associated with people who were considered to be sick in a sociological construct by Parsons (1958). The concept was expanded to include the term sickness behavior by Twaddle (1979) who, as seen above, previously addressed the triad of disease, illness, and sickness. More recently, descriptions of the specific behavior of diseased animals and humans as it relates to the consequences of infections and host responses to endogenously produced cytokines (Hart, 1988; Dantzer et al., 1998) also used the term sickness behavior (see Section 8). In infectious diseases, sickness behavior constitutes part of the disease process; it includes biological responses that are processed and perceived in turn as subjective symptoms. In modern immune concepts of disease, Twaddle’s concept of progression of disease to illness to sickness (Twaddle and Nordenfelt, 1994) could now be considered one of simultaneous events. In a classical medical model, tissue responses brought about by the actions of the infecting agent, the host’s responses to them, and the symptoms produced during these processes

constitute sickness or “the state of being sick or ill” (Oxford English Dictionary, 2007). In the current era and in particular in this essay, the recommended evaluation of patients with prolonged symptoms and their adverse consequences, must distinguish between the presence of an ongoing disease (active infection or ongoing tissue injury, illness, altered physiology, and sickness behavior) and an ongoing illness (illness behavior in the absence of tissue injury or apparent abnormal physiological function).

Ongoing inflammatory or infectious diseases may often be identified as such using standard laboratory tests, such as a CBC with differential, serum protein electrophoresis and assays for C-reactive protein, activation of the complement system, and quantitative determination of immunoglobulin isotypes in which test results vary from the norm in nonspecific patterns. Chronic active hepatitis C is an example of a disease manifesting sickness behavior in which these tests are consistently abnormal. In the absence of overtly abnormal findings in a person with prolonged duration of illness, it is common for practitioners to consider a psychological explanation during the clinical evaluation. Prolonged illness may follow disease initiated by infection or physical trauma, or by emotional and physical stress or by a process without apparent explanation.

4. Chronic fatigue syndrome: chronic infection or immune dysregulation?

Chronic fatigue syndrome (CFS) is one name for such an illness that may follow infectious diseases in subsets of patients (Fukuda et al., 1994). The syndrome is characterized by clinically unexplained fatigue of at least 6 months duration that is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities. The fatigue must be accompanied by at least 4 of 8 self-reported symptoms: (1) unusual post-exertion malaise, (2) unrefreshing sleep, (3) impaired short-term memory or concentration, (4) headaches of a new type, pattern, or severity, (5) muscle pain, (6) multi-joint pain without swelling or redness, (7) sore throat, and (8) tender cervical/axillary lymph nodes. The current CFS case definition relies entirely on self-reported symptoms and disability and specifies no standard measures. Recently, empiric criteria have been applied to the CFS definition, which include the severity of the patient’s impairment, fatigue, and symptoms (Reeves et al., 2005).

Because this symptom complex is the hallmark of CFS many inconclusive attempts to explain CFS on the basis of ongoing infections with specific infectious agents have been made since the mid-1980s (Jones et al., 1985; Straus et al., 1985) and as reviewed by Afari and Buchwald (2003), Jones et al. (2005), Devanur and Kerr (2006), and Komaroff (2006). Likewise, over 100 studies have investigated altered immune function in CFS as the cause of or a contributing factor to the syndrome. While many found immune alterations as potential explanations for the symptom complex or as possible predisposing factors in the production in altered responses to infections, the findings have not been consistent, and as reviewed by Gerrity et al. (2004) and

reflected in more recent reports (Houtveen et al., 2007) an ongoing cause and effect relationship between the syndrome and immunological processes has not been established.

5. Neuroendocrinologic findings in CFS

Possible neuroendocrine system changes in CFS, particularly in the hypothalamic–pituitary–adrenal (HPA) axis, were proposed by Demitrack et al. (1991) based on the similarity of symptoms in the syndrome to those seen in glucocorticoid deficiency states and they continue to be a subject of study regarding the genesis or maintenance of the syndrome. They found reduced basal evening glucocorticoid levels and increased basal evening ACTH concentrations, and low 24-h urinary free cortisol excretion. CFS subjects also demonstrated a diminished maximal response to administration of ACTH and an attenuated ACTH response to ovine corticotrophin-releasing hormone (CRH) administration. Reviews and additional studies addressing the HPA axis describe findings ranging from no differences between CFS subjects and control subjects to results that are similar to the initial observations (Hamilos et al., 1998; Cleare, 2004; Jerjes et al., 2006). Alteration in response to vasopressin infusion and a dehydroepiandrosterone sulfate deficiency have also been suggested (Altemus et al., 2001; Kuratsune et al., 1998). More recently, autonomic nervous system (ANS) responses that are closely linked to HPA function have been under scrutiny as contributing factors in the genesis of CFS (Bou-Holaigah et al., 1995; Stewart, 2000). One of the unexpected results in these studies was identification of a possible role for low serum aldosterone as contributing factor in orthostatic instability and heart variability in some individuals with CFS (Boneva et al., 2007). HPA axis changes in relationship to stressful events both preceding and accompanying a temporally associated triggering infection continue to be evaluated in these sickness syndromes (Heim et al., 2000 reviewed by Cleare, 2003; Tanriverdi et al., 2007) with a primary question being whether the changes in HPA axis measurements are primary or secondary. Fries et al. (2005) extend the discussion to include a purposeful role for low cortisol levels following a prolonged period of hyperactivity of the HPA in these conditions.

In retrospect, besides examination of the HPA axis in CFS because of similar illness expression, it is also important because of its role in control of immune responses to infection and to behavioral and physiological responses in general. Activation of the HPA axis during infection or stress, begins with release of CRH in both the central nervous system (CNS) and in peripheral tissues. It contributes to induction of behavioral responses (cerebral cortex and the amygdala), autonomic reactivity (fibers from the locus ceruleus to the brainstem), and hormonal responses via the HPA axis proper (Majzoub, 2006). A number of studies have provided evidence for possible impairment of glucocorticoid signaling in CFS (Rajeevan et al., 2007; Smith et al., 2006). CRH levels in the CNS by virtue of examining cerebrospinal fluid have not been evaluated in CFS, but their evaluation in fibromyalgia suggest a role in production of pain, but not in symptoms of fatigue (McLean et al., 2006).

6. Post-infection fatigue syndromes

Even with the lack of consistency among results in studies of immune and endocrine function associated with responses to infection, a majority of CFS cases identified by practitioners follow apparent virus infections (Afari and Buchwald, 2003). A well-studied example of a post-infection fatigue syndrome (PIF) is the illness following infectious mononucleosis described by White et al. (1998). To meet acute post-infection criteria, these patients were required to have physical fatigue for at least 2 weeks, two of five symptoms, including hypersomnia, poor concentration, psycho-motor retardation, irritability, or anhedonia, significant incapacity, and no co-morbid psychiatric disorder. An additional evaluation identified those who met the CFS definition criteria after 6 months. More recently, Hickie et al. (2006) have developed criteria for PIFs following acute EBV mononucleosis, acute Ross River virus, and acute Q-fever (*Coxiella burnetii*) infections that also fulfill CFS diagnostic criteria. Cameron et al. (2006) and Vernon et al. (2006) evaluated the above patients with post-infectious mononucleosis and could not identify unusual persistence of the virus nor explanatory changes in immune function. Such “failures,” however, may not preclude the presence of ongoing disease at levels that are not understood, but this essay will address this possibility based on the premise that the illnesses in question stem from responses to previous infections and not to ongoing viral or immunologic factors. It is of interest that Hickie et al. (2006) reported that the perceived magnitude of the initiating acute disease predicted the development of PIF. The concept that a preceding infection may trigger a chronic illness does not exclude a contribution to such an illness by responses to other insults associated with stress or injury (Heim et al., 2006 reviewed by Prins et al., 2006).

7. Immune responses to infection: review of the “immunological self” concept

Historically, both adaptive innate and innate immune responses revolve around self, defined here as the genetic qualities that identify the individual as being unique. Self in terms of the adaptive system can be traced back to writings of Burnet (1959) and others (reviewed by Langman and Cohn, 1996). But it was through the study of adaptive immune responses to viruses, however, that the concept of recognition of altered self became a central theme in the study of host responses to infection (Doherty and Zinkernagel, 1974). The adaptive system includes responses mediated by immunoglobulin or T cell receptors that were generated by gene rearrangements in lymphocytes during fetal development and subsequently recognize peptides or protein configurations derived from infecting organisms in conjunction with self proteins (the original “altered self” in immunological parlance). Once activated, the adaptive immune response triggers a variety of cell populations to respond with production of antibodies, cell-cell interactions, and release of effector molecules, such as IL-1 β , tumor necrosis factor (TNF)- α , IL-6, interferon (IFN)- γ , etc.

The innate immune system is composed of circulating or cell-associated proteins encoded by genes that do not

undergo programmed rearrangements and that do not require prior exposure to cognate ligands for expression. This system consists of antimicrobial products (i.e., cathelicidins and defensins) found in epithelial and phagocytic cells, the complement system, cytokines, natural killer cells, microglia cells in the CNS, and subsequent phagocytic cell ingestion and killing of micro-organisms. The cell surface interaction of mononuclear cells and some epithelial cells with their respective target molecules is mediated by toll-like receptors (TLR) that bind to structurally conserved structures on microbes, such as lipopolysaccharides and peptidoglycans, and to cell proteins and are known as pathogen-associated molecular patterns. Activation of each of the individual components and their downstream counterparts by exposure to “non-self” or “absence of self” leads to release of molecules that participate in control of infection or other non-self targets via inflammation and illness production via stimulation of the sickness response (Medsharov and Janeway, 2000; Janeway and Medsharov, 2002; Tosi, 2005).

More recently, Matzinger (2002) proposed a “danger” model in which specific recognition of foreign proteins (“non-self” or “altered self”) is not driving the host response to infection or injury. Rather, it is recognition of the insult as “danger” that triggers the collective host responses. The danger system utilizes the components of both the innate and adaptive immune systems. Exposure of tissue antigen presenting cells to endogenous or to non-foreign “alarm signals” (e.g., DNA or RNA, heat shock proteins, or cytokines), released or generated as a result of injury, constitutes a “damage” control system. In the “danger” response concept, altered self occurs as a consequence of injury and/or exposure to endogenous substances that are usually sequestered. The involved tissue apparently dictates the level and type of subsequent immune response. In all of these views the immune response is triggered by foreign molecules, altered self, or by “damage” and is amplified by a cascade of inflammatory and metabolic events. It is curious that some of the danger-associated substances, such as extra-cellular heat shock proteins, also induce immunological and physiological responses when produced in psychological stress models (Fleshner and Johnson, 2005). In terms of this discussion, the end result is production of what we consider disease or illness and their shared behavioral responses.

8. Sickness behavior and interferons

Sickness behavior is hypothesized to confer a biological advantage to the sick animal (Hart, 1988). The overarching response is diminished physical and mental activity thereby sparing of energy usually available for activity and “shunting” of energy reserves for production of new proteins, alteration of glucose and lipid metabolism, fever, increased thyroid metabolism, and HPA-mediated maintenance of cell and organism integrity and modification of transcription. Peters et al. (2004) consider the physiological changes to be under control of “the selfish brain,” where the brain regulates all illness responses in order to insure adequate energy for maintenance of its function. Physical and mental inactivity may be associated with irritability and aggressive

behavior leading to isolation from others (Hart, 1988; Zalcman and Siegal, 2006), consequences that may be beneficial for survival for both the individual (Hart, 1988; Dantzer and Kelley 2007) and theoretically for others in the sick individual's immediate living or working group (Hart, 1988), since humans and animals avoid contact with individuals demonstrating such behavior. Decreased contact by the sick individual with others presumably prevents spread of the infectious agent and limits energy expenditure enhancing resolution of the infection. Therefore a societal benefit for disease-associated sickness behavior, as well as sickness being recognized as a sociological construct, is certainly possible.

The therapeutic use of IFNs α/β and γ induces fever, chills, and symptoms of sickness behavior including malaise and anorexia, which appear within 24 h following injection and subsequently diminish over the following weeks (Raison et al., 2005). Mood changes along with symptoms often attributed to neuropsychiatric diseases (primarily depression) (Reite et al., 1987; Wichers and Maes, 2002; Raison et al., 2006), such as sleepiness, loss of appetite, cognitive problems, and long-lasting fatigue, occur later in the course of treatment with these biologic response modifiers and may persist or increase in magnitude over the duration of therapy (Wichers and Maes, 2002; Maddock et al., 2005).

Studies of subjects with cancer and chronic virus infections manifesting acute sickness behavior and particularly symptoms of depression, during and following treatment with IFNs with and without antiviral medication, for example, have identified a series of vulnerability factors (Capuron and Miller, 2004; Raison et al., 2005). The major factor is the pretreatment presence of subclinical symptoms of depression, including sadness, pessimistic thoughts, and sleep disturbances. A second finding was activation of corticotropin-releasing factor and hyper-responsiveness of the HPA axis manifested by elevated levels of ACTH, and cortisol following the initial injection of IFN. A more recent study in subjects with multiple myeloma also identified pre-treatment levels of soluble IL-6 receptor (IL-6R) and soluble tumor necrosis factor- α receptor 1 (TNF-R1) as being predictive of IFN- α -induced depression scores (Friebe et al., 2007). Of potential interest is the origin of the preclinical symptoms (sadness, pessimistic thoughts, and sleep problems) and their possible relationship to the diseases under therapy that obviously involve immunological processes and perceptions of the consequences of the diseases under treatment.

Although the molecular mechanisms underlying the production of any symptom following IFN therapy are unclear (Kaiser et al., 2001; Konsman et al., 2002), changes occur in the metabolism of the prefrontal cortex identified by PET studies (Juengling et al., 2000) and in information processing in the anterior cingulate cortex as determined by fMRI studies (Capuron et al., 2005). These findings raise the issues of a direct effect of cytokines in the brain in the production of sickness behavior or whether IFN-related changes induced in the periphery and detected in the brain affect CNS responses (Watkins and Maier, 2005).

9. Neuroscience, immunity, and self

In April 2002, the journal *Science* introduced an expanded concept the topic of self in a series of papers presented

under the title of "Reflections of self: immunity and beyond," two of which are cited above (Medshinov and Janeway, 2002; Matzinger, 2002). A third paper by Churchland (2002a) described the self in terms of representation in the CNS and stimulated much of the thought behind this essay. Churchland's message is that the brain has self-representational capacities that have arisen through evolution for detection and processing of inner body signals in order to choose optimum behavioral strategies. Some of these strategies are purely neurochemical (unconscious) and others require cortical (conscious) processing of the neurochemical signals. Included in this process are brain sites that monitor various components of bodily function. To briefly paraphrase Churchland's (2002b) description: the signals related to changes in blood chemistries, hormones, and mediators/effectors of immunity from the viscera and other internal sites are monitored in several areas of the brain: musculoskeletal structures in the broad somatosensory pathway; autobiographical events in the medial temporal lobe; and control of impulses and delaying gratification in the prefrontal cortex and limbic systems. Tracey (2002) also includes the effects of immune responses as afferent signals and considers their interaction with the nervous system as the "inflammatory reflex." Thus a complete picture of past infections, in terms of biological events and their consequences is monitored, recorded, and processed in the brain; in essence, they are "remembered."

Craig (2002) and Mayer et al. (2006) reviewed this process, also known as interoception ("the sense of the physiology of the body" or "how do you feel?"), as transmitted through small diameter sensory afferent fibers or "homeostatic afferents" to and through a brain network. Critchley et al. (2004) and Critchley (2005) described the neural pathways underlying awareness of bodily functions and considers a composite model of autonomic, affective, and cognitive factors as necessary for gaining understanding of these complex relationships. Using a variety of somatic and self-monitoring stimuli (challenges) these authors and many others have used brain imaging to map in detail the ascending and descending pathways associated with self-monitoring, their subsequent re-representation in the insular cortex, and afferent signaling, particularly through the ANS. Just as there are anatomical areas associated with interoception, Northhoff and Bermpohl (2004) identified anatomic components of the self in the brain and identified several cortical midline structures composing an anatomical unit, as well as lateral structures such as the right prefrontal and parietal cortices. The midline components include orbital and adjacent medial prefrontal cortex, the anterior cingulate cortex, the dorsomedial prefrontal cortex, and the posterior cingulate cortex. These areas connect with each other and with structures in the midbrain and brainstem subserving autonomic function, and with the limbic system structures including the hippocampus, amygdala, hypothalamus, and as mentioned previously, the insular cortex. The reader is referred to Craig (2002), Mayer et al. (2006), and Northhoff and Bermpohl (2004) for depictions of these anatomic areas and neural pathways.

In humans, physical experiences are also seen at an emotional level suggesting interconnections between interoceptive pathways and centers of emotion (Damasio, 1996, 1999; Cameron, 2001; Churchland, 2002a). Wiens (2005)

reviewed this topic and describes physiological studies, such as heartbeat detection and functional magnetic resonance imaging (fMRI studies that support functional anatomic relationships). In a single report of a restricted disease paradigm, Rosenkranz et al. (2005) questioned the role of emotion in asthma symptom exacerbation and found changes in activation in the anterior cingulate cortex and the left insular cortex using functional magnetic resonance imaging. They found that activity in the anterior cingulate cortex and insula to asthma-relevant emotional, compared with valence neutral stimuli, is associated with markers of inflammation and airway obstruction in asthmatic subjects exposed to antigen. Unlike the illnesses addressed in this essay, their findings were limited to asthma, a specific, but complicated, peripheral process with readily identifiable pathology. More recently, Vollmer-Conna et al. (2006) brought the term interoception into the clinical arena of CFS by referring to a subset of CFS subjects as having an "interoceptive profile" based on their identification of subjective symptoms including fatigue, sleep disturbances, pain, and depression.

Just as the biological processes are recorded in the brain, the sensations and consequences of sickness behavior are remembered. Most adults can conjure up the feelings and sensations they experienced when having an influenza infection, infectious mononucleosis, or another systemic virus infection. Since infections and immunizations begin early in childhood, it is possible that such memories (conscious and unconscious) are stored indefinitely. In fact, young children can relate current illness symptoms to episodes experienced at earlier ages. As we will discuss, the question of stored physiological experiences that exist below consciousness may impact behavior as well.

10. Self, altered self, and extended altered self

The concept of self can be discussed in several disciplines (Churchland, 2002b). The psychological self (Brown, 1999; Miller et al., 2001) describes the essential qualities that distinguish one person from another and equate to the total, particular being of the person. It provides a sense of integrity for diverse experiences. The conscious recognition of these events, or feelings so produced, reflect the temporal and spatial unity we perceive as self. The self at both neurological and psychological levels allows the individual to adapt and to do what is needed in any situation. The function of these "selves" also depends on autobiographical memories, including those of physical effects triggered by host responses to "damage," infection, and inflammation. Note that these perceptions are based in part on biological responses that are reflected in feelings and their consequences.

Self in philosophical terms provides an extra, but vital dimension to the discussion. The Oxford English Dictionary defines self as "that which in a person is really and intrinsically he or she" and that it is what the individual "is at a particular time" with different attributes assigned/assumed "as different at different times" (Oxford English Dictionary, 2007). Note the relationship between this tenet and Churchland's emphasis on self-representation in the

brain as necessary for the organism's ability to respond at any time most appropriately to its environment. Northoff (2004) discusses in detail relationships between the science and philosophy of the brain as they apply to the study of brain function.

All of these constructs of self are dependent on representation of ongoing physiological and psychological processes in the brain and on changing patterns of activity that process and transmit information at multiple levels. Churchland (2002a) describes the process as a collection of "capacities" and/or their "utilization." They represent a "fundamental capacity" or its coordination of needs when confronted with new situations, perception of new situations, or their memory. Therefore, humans need intact, functioning selves in order to interpret events (past experiences), to carry out daily activities, and to plan future activities as individuals and as members of a society. Functional self, therefore, is the reference point from which all subsequent responses to any noxious or non-noxious stimuli emanate (Churchland, 2002b). The term "altered self" is based on altered cell surface proteins produced during a virus infection, but in this essay is extended to include each or all of the above self constructs. It suggests both a state required for successful responses to a challenge or in the case of a prolonged illness, a failure to adapt to a different state.

11. Synthesis and hypotheses

The following statements can be made:

1. In infections that lead to disease and sickness, altered self can be considered a basis of recognition by and activation of innate, adaptive, and/or danger-driven immune responses and general self-maintenance responses.
2. The subsequent immune system and organ system functional changes induce physiological and biochemical alterations that are also recognized at multiple brain levels as extended altered self.
3. Specific organ-based signs, symptoms, and behaviors produced during an infection constitute expression of disease.

Based on these statements the following hypotheses can be generated:

1. In diseases with sickness behavior, brain responses occur at the unconscious (physiological/subcortical or innate) level and the conscious (cortical or adaptive) level with the aim of restoring host stability and resolving the altered self state.
2. Resolution of disease or illness requires successful adaptation to the insult.
3. Disease and illness can occur simultaneously, but resolution of each may follow different time courses.
4. Continued disease is associated with uncontrolled infection, altered immune responses, or ongoing injury. Persistent illnesses such as CFS and post-infection fatigue are due to maladaptive biological (interoceptive) and/or cortical signal recognition or subsequent responses to them.

Thus in chronic illness following infection in the absence of readily identifiable markers of immunologically mediated injury or responses, the extended concept of altered self means the individual has strayed from their baseline stability or positive adaptive capabilities due to perturbations in the production or recognition of biological signals.

In addition to the need for delineation of neural networks underlying interoception, further exploration of the extended altered self model in chronic sickness, such as CFS and PIF, requires a partial listing of possible for "self-representation receptors" including non-self/altered self products or immune/inflammatory system products as described by Tracey (2002) and Maier (2003) and components of the innate immune system such as peripheral and brain microglial cells (Watkins et al., 2007) and astrocytes (Farina et al., 2007) and their signals or "ligands": consequences or "products of exercise"; ANS signals or products; hormonal products of the stress response; and biological consequences of altered sleep. One may also question the role of both conscious and unconscious "memories" of the "ligand" binding and subsequent events described above as to whether they might serve as primary signals or amplifiers of the system. These questions extend the discussion to include the additional dimension of conditioning as in studies of the induction of sickness behavior by non-immune stimuli (extensively reviewed in Dantzer, 2001 and Dantzer and Kelley, 2007). Thus, do the immune mediators and their biological effects or can the memories of those effects when experienced again elicit sickness behavior or illness symptoms?

12. Research questions

Testing of the concept of extended altered self as proposed here should lend itself to a wide spectrum of experimental approaches. Perhaps the most obvious questions are: How can the self or its components (immunological, psychological, philosophical, and/or neurological) that are involved in illness production be identified and measured, and can these variables be targeted for study or intervention? Currently, as seen above, many studies of acute and chronic diseases or illnesses, such as CFS, approach individual or integrated organ systems (immune system, HPA axis, and the ANS) by examinations beginning with the genome and extending to their afferent or efferent products in the effort to identify origins of illness (Steinau et al., 2004; Vernon and Reeves, 2006). I will limit questions in the current discussion to whether the brain should also be considered an appropriate target for examination using a "top-down" functional approach, and secondly, to whether the brain can be a target for subsequent intervention and at which level(s)? One can test the altered self concept with baseline and challenge studies of the functional pathways in the brain using a variety of modalities, including imaging techniques such as fMRI before, during, and after performance of appropriate tasks with current computational analyses by comparing well-defined patients and control subjects. As mentioned above, anatomical areas associated with self processing have been identified using PET and fMRI imaging (Craik et al., 1999; Fossati et al., 2003; Macrae et al., 2004; Northoff et al., 2006), as have neural pathways associated

with interoception as reviewed by Craig (2002). These areas overlap considerably with areas of the brain associated with emotion, an important component of illness expression as alluded to through this essay (Davidson, 2004). Tasks that examine the relationships in function of these areas and other areas could include exposure to stressful memory-based tasks such as either letter- or number-based n-back tests (Goldberg et al., 2003; Harvey et al., 2005) a paradigm that would also test complaints of altered memory in CFS and PIF subjects, and confrontation with words that evoke illness responses during fMRI testing (Kircher et al., 2000). These and other tasks would also impact ANS function, a critical component of interoceptive pathways, as considered by Critchley et al. (2004) and Critchley (2005), thus exposing the brain to stimuli that might be operative in producing altered self responses. Measurement of subsequent changes in brain activation, however, is complex. As placed in perspective by Critchley (2005), the efforts must be viewed in the context of whole body resting state physiology and examination of these specific brain regions must be performed with consideration of brain areas active in the resting state and during functional tasks, thereby allowing assessment of overall coordinated brain function or functional connectivity (Cordes et al., 2000). Newer mathematical approaches may allow evaluation of the temporal characteristics of connectivity (Rajapakse and Zhou, 2007), a reasonable approach while developments in measurement of function and imaging technology begin to catch up with needs in the field (Montoya et al., 2006; Westmeyer and Jasanoff, 2007).

Such studies in persons with chronic illness manifested by sickness behavior (CFS and PIF) in the absence of disease as defined above may demonstrate consistent changes in baseline fMRI values (increased or decreased activity) compared to asymptomatic persons. Or specific challenges may lead to differential changes in magnitude or direction of activation in regions such as the insular cortex, orbito-frontal cortex, anterior/posterior cingulate cortex, or higher cortical regions. If alterations in interoceptive processes associated with ANS function (i.e., heart rate, galvanic skin responses) in the above areas, particularly in the self-referential areas, were found, would they respond to "bottom-up" pharmacological intervention, biofeedback, or meditation aimed at influencing "innate" biological responses? Or if altered activation in higher cortical regions was preferentially present or combined with changes in lower areas, would cognitive-behavioral therapy (CBT), a "top-down" therapy, or combined therapy be more effective for these "adaptive," "learned," or conditioned responses? It is of interest that CBT remains an effective therapy for CFS without specific understanding of its mode of action (Whiting et al., 2001; Deary et al., 2007). At any level of therapy the ultimate goal is directed intervention in chronic illness states in order to break the "circle" of chronic sickness behavior due to altered self with return to a functional self state capable of responding to current and future challenges (Figure 1).

These paradigms and specific questions are based in part on the work of Helen Mayberg and colleagues who have used imaging techniques to identify activation of different brain regions in patients with depression who have conjured up their worst perceptions of depression (Mayberg et al., 1999).

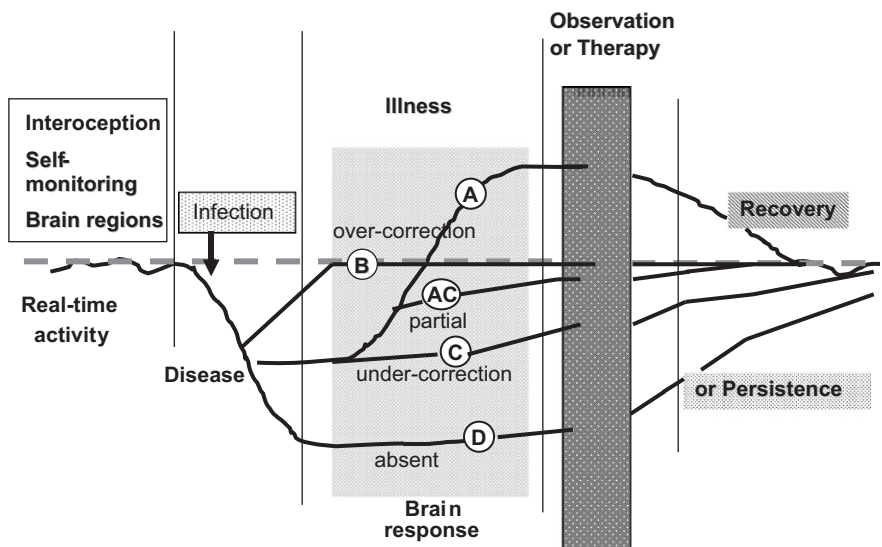


Figure 1 Functional brain imaging: seeing “insult” and ongoing compensation. This figure serves multiple purposes. The box at the left represents baseline self monitoring as an interoceptive self network. The box in the center of the figure represents the range of brain responses to the challenge situation, in this case an infection: A = overcorrection, B = correct response, AC = partial correction, C = under-correction, and D = absence of a response. The long rectangular box reflects observation of the individual or introduction of therapy. The solid black lines display real time cumulative brain activity associated with interoception as recorded by fMRI compared to the ideal baseline activity represented by the dotted line during the possible courses of an illness complete with idealized outcomes. Adapted with permission from Mayberg (2003b).

Subsequently individuals with different brain activation patterns respond accordingly to medication versus cognitive behavioral therapy (Mayberg, 2003a).

13. Concluding remarks

Chronic illnesses, such as CFS and PIFs, in the absence of evidence of standard mechanisms of pathogenesis, require new concepts of illness origin. In illnesses that follow infection, symptoms that were initiated as the consequence of innate and/or adaptive immune system responses may be perpetuated by ongoing alterations in a normally positive dynamic self construct. Approaching such alterations by studying the function of the brain using a “top-down” paradigm may offer clues to the generation of the illness and sites for targeted therapy. The extended altered self model might also apply to the study of other stress-associated and somatic illnesses, but this essay is designed to generate discussion and not to describe in detail all possible avenues of investigation of the topics at hand.

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Conflict of interest

None declared.

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