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Cytokine-Induced Sickness Behavior: Mechanisms and Implications

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ABSTRACT: Sickness behavior refers to a coordinated set of behavioral changes that develop in sick individuals during the course of an infection. At the molecular level, these changes are due to the brain effects of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNFα). Peripherally released cytokines act on the brain via a fast transmission pathway involving primary afferent nerves innervating the bodily site of inflammation and a slow transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs and diffusing into the brain parenchyma by volume transmission. At the behavioral level, sickness behavior appears to be the expression of a central motivational state that reorganizes the organism priorities to cope with infectious pathogens. There is evidence that the sickness motivational state can interact with other motivational states and respond to nonimmune stimuli probably by way of sensitization and/or classical conditioning. However, the mechanisms that are involved in plasticity of the sickness motivational state are not yet understood.

INTRODUCTION

Nonspecific symptoms of infection and inflammation include fever and profound physiological and behavioral changes. Sick individuals experience weakness, malaise, listlessness, and inability to concentrate. They become depressed and lethargic, show little interest in their surroundings, and stop eating and drinking. This constellation of nonspecific symptoms is collectively referred to as "sickness behavior". Due to their commonality, sickness symptoms are frequently ignored by physicians. They are considered as an uncomfortable, but rather banal, component of the pathogen-induced debilitation.

This view is, however, totally inadequate. The behavioral symptoms of sickness represent, together with the fever response, a highly organized strategy of the organism to fight infection.[1] In physiological terms, fever corresponds to a new homeostatic state that is characterized by a raised set point of body temperature regulation. A feverish individual feels cold at usual environmental temperatures. Therefore, the feverish person not only seeks warmer temperatures, but also enhances heat production (increased thermogenesis) and reduces heat loss (decreased thermolysis). The higher body temperature that is achieved during fever stimulates proliferation of immune cells and is unfavorable for the growth of many bacterial and viral patho-

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gens. In addition, the reduction of zinc and iron plasma levels that occurs during fever decreases the availability of these vital elements for growth and multiplication of microorganisms. The adaptive nature of the fever response is apparent from studies showing that organisms infected with a bacteria or virus and unable to mount an appropriate fever response because they are kept in a cold environment or treated with an antipyretic drug have a lower survival rate than organisms that develop a normal fever.[2]

The amount of energy that is required to increase body temperature during the febrile process is quite high since, in human beings, metabolic rate needs to be increased by 13% for a rise of 1°C in body temperature. Because of the high metabolic cost of fever, there is little room for activities other than those favoring heat production (e.g., shivering) and minimizing thermal losses (e.g., rest, curl-up posture, piloerection).

In recent years, evidence has rapidly accumulated to demonstrate that the necessary synchrony between metabolic, physiological, and behavioral components of the systemic response to infection is dependent on the same molecular signals as those that are already responsible for the local inflammatory response. These signals are proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and interferons (IFNs), that are released by activated monocytes and macrophages during the course of an infection. These cytokines act on the brain in two successive waves: a first wave that is triggered by activation of primary afferent neurons innervating the body site where the inflammatory reaction takes place and a second wave that involves slowly diffusing cytokines from the circumventricular organs and choroid plexus to brain targets such as the amygdaloid complex.

Although sickness behavior is a normal response of the host to pathogens that are recognized by the innate immune system, there is evidence that sickness behavior can be triggered by nonimmune stimuli, in the same way that sickness behavior can alter the organism response to environmental stressors.

CYTOKINES INDUCE SICKNESS BEHAVIOR

Systemic or central infusion of recombinant cytokines induces the full-blown repertoire of nonspecific symptoms of sickness in both experimental animals and human beings. The same effects are obtained in response to the administration of molecules that induce the synthesis of endogenous cytokines [e.g., lipopolysaccharide (LPS), the active fragment of endotoxin from gram-negative bacteria].

The behavior of animals injected with LPS or cytokines at the periphery or into the lateral ventricle of the brain has been studied extensively.[3] Rats injected with LPS or IL-1β after drinking a new taste solution develop a conditioned aversion to the taste of that solution.[4,5] Conditioned taste aversions have also been established to TNFα. However, treatment with IFNα fails to induce conditioned taste aversion.[6] The reasons for these differences between cytokines are still unclear.

Decreased social exploration of juvenile conspecifics has been used as a convenient way to assess sickness behavior in laboratory rodents. It involves olfactory sampling of the partner and is normally used for social recognition. It offers the advantage of being reproducible and quantifiable. The use of juvenile conspecifics

helps to keep at a minimum the emergence of other behavioral patterns such as sexual behavior or aggression normally occurring with adult partners. Systemic administration of LPS, IL-1β, and TNFα to adult laboratory animals, rats, or mice consistently decreases the time spent in exploration of juveniles.[7–9]

Another important component of sickness behavior is the decreased intake of food that develops in sick individuals. Systemic administration of IL-1β and TNFα consistently suppresses feeding. This effect has been observed using various measurements of food intake under *ad libitum* as well as deprived conditions.[10,11] In contrast to the decrease in social exploration that takes about 2 hours to develop, the suppression of food intake occurs within 1 hour following treatment.

NEUROANATOMICAL BASIS OF SICKNESS BEHAVIOR

Our understanding of the way that sickness behavior is organized in the brain is based on several methodological approaches. Molecular biology studies have demonstrated that peripheral cytokines induce the synthesis and release of cytokines in the brain. LPS, for instance, induces the expression of IL-1α, IL-1β, and TNFα, followed by that of IL-6.[12,13] The main cellular sources of IL-1 are represented by microglial cells and perivascular and meningeal macrophages.[14] These locally produced cytokines are responsible for the central components of the host response to infection, as demonstrated by pharmacology experiments making use of cytokine antagonists or cytokine receptor antagonists. For instance, administration of the IL-1 receptor antagonist (IL-1ra) into the lateral ventricle of the brain to block brain IL-1 receptors abrogated the depressing effect of peripherally administered IL-1 on social exploration in rats exposed to a juvenile.[15] Using expression of the early gene *c-fos* as a marker of neuronal activation in those brain areas that are activated by stressors, neuroanatomists have identified the brain targets of peripheral immune stimuli. Wan *et al.*[16] were the first authors to show that intraperitoneal injection of LPS activates the primary projection area of the vagus nerve in the brain, which is represented by the nucleus tractus solitarius, and the secondary projections of this nerve, including the parabrachial nucleus, the hypothalamic paraventricular and supraoptic nuclei, the central nucleus of the amygdala, and the bed nucleus of the stria terminalis. A subdiaphragmatic section of the vagus nerves abrogated the expression of Fos in these brain areas. The key role of the vagus nerve in the transmission of peripheral immune signals to the brain was further confirmed by the demonstration that vagotomy attenuates the behavioral actions of peripheral cytokines[17,18] and abrogates the induction of IL-1β in the brain in response to peripheral LPS or IL-1β.[19,20]

The abdominal vagus nerve has the important peculiarity of being associated with immune cells that express IL-1β in response to local inflammation.[21] This locally produced IL-1β binds to vagal fibers to increase vagal discharge activity. Glutamate is released at the level of the nucleus tractus solitarius (NTS) where vagal fibers terminate.[22] Glutamate acts on catecholaminergic neurons of the NTS that project to the paraventricular and preoptic nuclei.[23,24] The central nucleus of the amygdala can be reached via this pathway or, more probably, via the parabrachial nuclei.[25] These pathways appear to be responsible for the activating effects of inflammatory stimuli on the hypothalamic-pituitary-adrenal (HPA) axis and their depressing effects on

behavior. However, the pyrogenic activity of inflammatory stimuli involves still another pathway represented by prostaglandin synthesis by cyclooxygenase-2 around blood vessels.[26]

The brain production of IL-1β in response to peripheral inflammatory stimuli is first restricted to the choroid plexus and circumventricular organs.[27] It then slowly diffuses to the brain side of the blood-brain barrier by volume transmission. Direct activation of neurons by slowly diffusing IL-1β takes place in the basolateral amygdala and the area postrema. Projections from the basolateral amygdala mediate the depressing effects of IL-1β on social exploration, whereas those from the area postrema contribute to activation of the HPA axis.[28] The observation that a late (4 hours post-LPS) infusion of IL-1ra into the lateral ventricle of the brain attenuates the depressing effects of systemic LPS on social exploration concomitantly with an abrogation of Fos expression in the central amygdala and bed nucleus of the stria terminalis points to the role of these two structures in cytokine-induced behavioral depression.[28]

In summary, activation of afferent nerve fibers by peripherally released cytokines represents a fast pathway of transmission of immune signals from the periphery to the brain. This pathway certainly sensitizes the brain target areas to the action of brain-produced cytokines that relay and amplify the action of peripheral cytokines.

MOTIVATIONAL ASPECTS OF SICKNESS BEHAVIOR

Sickness behavior is usually viewed by physicians as the result of debilitation and physical weakness that inevitably occur in an organism whose all resources are engaged in a defensive process against pathogens. An alternative hypothesis is that sickness behavior is the expression of a highly organized strategy that is critical to the survival of the organism. If it is the case, then it follows that sick individuals should be able to reorganize their behavior depending on its consequences and the internal and external constraints they are exposed to. This flexibility is characteristic of what psychologists call a motivation. A motivation can be defined as a central state that reorganizes perception and action. A typical motivational state is fear. In order to escape a potential threat, a fearful individual must be attentive to everything that is occurring in his/her environment. At the same time, he/she must be ready to engage in the most appropriate defensive behavioral pattern that he/she has available in his/her behavioral repertoire. In other terms, a motivational state does not trigger an unflexible behavioral pattern. It enables one to uncouple perception from action and therefore to select the appropriate strategy depending on the eliciting situation.[29]

The first evidence that sickness behavior is the expression of a motivational state rather than the consequence of weakness was provided by Miller.[30] He showed that rats injected with endotoxin stopped bar-pressing for water, but, when given water, drank it, although to a lesser extent than normally. This effect was not specific to thirst since the endotoxin treatment also reduced bar-pressing for food and even blocked responding in rats trained to press a bar for the rewarding effects of electrical stimulation in the lateral hypothalamus. Interestingly enough, when rats were trained to turn off an aversive electrical stimulation in this brain area, endotoxin also reduced the rate of responding, but to a lesser extent than bar-pressing for a reward-

ing brain stimulation. However, when rats were placed in a rotating drum that they could stop for brief periods by pressing a lever, endotoxin treatment resulted in an increase rather than a decrease in their response rate. The mere fact that endotoxin treatment could decrease or increase behavioral output depending on its consequences gave strong support to the motivational interpretation of the behavioral effects of such a treatment.

An example of behavioral reorganization in response to sickness is provided by the effects of LPS on macronutrient intake. When rats are given the opportunity to select components of their diet, their selection pattern reflects the organism's nutritional and energetic requirements. To determine whether this selection pattern is altered during sickness, rats were submitted to a dietary self-selection protocol in which they had free access to carbohydrate, protein, and fat diets for 4 hours a day.[31] After a 10-day habituation to this regimen, they were injected with LPS or IL-1β. Under the effect of this treatment, they decreased their total food intake, but reorganized their self-selection pattern so as to ingest relatively more carbohydrate and less protein, whereas fat intake remained unchanged. This change in macronutrient intake contrasts with the increased fat intake that occurs in rats exposed to cold. Although eating fat would be a better way for feverish animals to cope with their increased energy requirements, it would not be of much use since cytokines have adverse metabolic effects resulting in increased lipolysis and hypertriglyceridemia. Under these conditions, an increased intake of fat would actually be counterproductive since it would further enhance hyperlipidemia without positively contributing to lipid metabolism.

An important characteristic of a motivational state is that it competes with other motivational states for behavioral output. The normal expression of behavior requires a hierarchical organization of motivational states that is continuously updated according to circumstances. When an infection occurs, the sick individual is at a life or death juncture and his/her physiology and behavior must be altered so as to overcome the disease. However, this is a relatively long-term process that needs to make room for more urgent needs when necessary. It is easy to imagine the following: if a sick person lying in his/her bed hears a fire alarm ringing in his/her house and sees flames and smoke coming out of the basement, he/she should be able to momentarily overcome his/her sickness behavior to escape danger. In motivational terms, fear competes with sickness, and fear-motivated behavior takes precedence over sickness behavior. An example of this competition between fear and sickness is provided by the observation that the depressing effects of IL-1β on behavior of mice are more pronounced when experimental animals are tested in the safe surroundings of their home cage than when they are placed into a new environment.

Another example of the motivational aspects of sickness behavior is the effect of cytokines on maternal behavior. If fitness is the key issue, it is evident that dams should care for their infants despite sickness. In motivational terms, the components of maternal behavior that are crucial for the survival of the progeny should be more resilient, that is, less sensitive to the depressing effects of pyrogens, than those behavioral patterns that are less important. In accordance with this prediction, administration of LPS to lactating mice did not disrupt pup retrieval, but impaired nest-building.[32] However, LPS treatment was less effective in depressing nest-building when the dams and their litters were exposed to 4°C, increasing the fitness value of nest-building, than when dams were tested at 20°C.

To show that sickness does not interfere with the subject's ability to adjust his/her behavioral strategies with regard to his/her needs and capacities, Aubert *et al.*[33] assessed the effects of LPS on food hoarding and food consumption in rats receiving or not a food supplement in addition to the amount of food they obtained in the situation. Rats were trained to get food for 30 min in an apparatus consisting of a cage connected to an alley with free food at its end. In this apparatus, rats normally bring back to their home cage the food that is available at the end of the alley and the amount of food they hoard is lower when they receive a food supplement than when they have no supplement. In response to LPS, food intake was decreased to the same extent whether rats received a food supplement or not. However, food hoarding was less affected in rats that did not receive a food supplement compared to rats provided with the food supplement. These results indicate that the internal state of sickness induced by LPS is more effective in suppressing the immediate response to food than the anticipatory response to future needs.

SENSITIZATION AND CONDITIONING OF CYTOKINE-INDUCED SICKNESS BEHAVIOR

Repeated injections of TNFα lead to different results depending on the interval between injections.[34] In animals injected with a subeffective dose of the cytokine, administration of TNFα at 1–7 days later was associated with a lowered response or a lack of response. However, lengthening the interval to 14–29 days resulted in an enhancement of the sickness response.

Instances of cross-sensitization between cytokines and nonimmune stressors have been reported, using the pituitary-adrenal response as an endpoint. Adult rats injected with a single dose of IL-1β and exposed 1 to 2 weeks later to a novel environment displayed a heightened reactivity of the pituitary-adrenal axis to novelty.[35] Similar long-lasting (1–12 weeks) sensitization of the pituitary-adrenal axis response to IL-2 has been reported in humans.[36] In the first case, the enhanced reactivity of the HPA axis has been shown to be mediated by an increased expression of vasopressin in the hypothalamic neurons that normally predominantly express corticotropin-releasing hormone (CRH).[35]

The possibility that sickness behavior can be triggered by nonimmune stimuli has been studied using mainly behavioral conditioning. Most of the studies have focused on the febrile response to LPS. In a typical experiment carried out in rats, LPS was used as an unconditioned stimulus in a taste aversion model using the taste of a saccharin solution as the unconditioned stimulus. LPS induced an initial fall in body temperature followed by an increase. The same pattern, although less marked, was observed in rats reexposed to the saccharin taste solution at 2 weeks after conditioning.[37] Conditioning of the febrile response has also been observed in mice exposed to a camphor odor paired with administration of the interferon inducer poly I:C.[38] In this study, one conditioning session was sufficient for conditioning-increased body temperature in young and old mice, and this conditioned response was quickly extinguished following a second reexposure to the conditioned stimulus. The possibility that conditioning extends to other components of the sickness response has been examined in a number of studies. Rats responded to saccharin paired with LPS by displaying a conditioned decrease in food intake,[39] as well as a conditioned sup-

pression of splenocyte IL-2 production and splenic norepinephrine content concomitantly with a conditioned enhancement of plasma corticosterone levels.[40] All components of the sickness response to LPS are not conditionable to the same extent since rats reexposed to saccharin paired with LPS displayed a conditioned febrile response, but not the typical increased slow-wave sleep and decreased REM sleep observed in LPS-treated animals on the conditioning day.[41] However, since this experiment was carried out during the light portion of the dark-light cycle, the possibility that the somnogenic components of the acute phase response are conditionable was retested by reexposing rats to the saccharin taste solution during the dark portion of the light-dark cycle.[42] This resulted in a conditioned increase in slow-wave sleep, but no change in REM sleep. All these findings appear at first glance to provide a demonstration of the conditionability of the sickness response. However, the interpretation of this phenomenon is not as straightforward as it appears a priori, especially since, at least in the case of body temperature, conditioned changes in body temperature were observed in rats exposed to saccharin paired with lithium chloride instead of LPS.[37] Thus, there is clearly a need for further investigation of the modalities and specificity of conditioning influences on sickness behavior.

PSYCHOPATHOLOGICAL IMPLICATIONS OF THE EXISTENCE OF A MOTIVATIONAL STATE OF SICKNESS

The demonstration that the immune system is able to influence behavior and mental states has important implications for our understanding of the relationships between psychological factors and disease. In the case of cancer, for example, such psychological features as the feelings of hopelessness and helplessness that are commonly associated with the onset and progression of the disease might be secondary to the effects on the central nervous system of factors released from immune or tumor cells during the early stage of the neoplastic process. The same possibility applies to the relationship between psychological factors and autoimmune diseases. The possible causal role of cytokines in the mental and behavioral symptoms that occur in various pathological conditions has hardly been investigated, except in a few cases, such as infection and fever, cachexia, AIDS dementia complex, chronic fatigue syndrome, and depression.

There is already evidence demonstrating that proinflammatory cytokines are responsible for the development of subjective and behavioral symptoms of sickness during infection with a bacterial or viral pathogen. For instance, patients treated with IFNα show fever, anorexia, fatigue, headache, myalgia, and arthralgia. These symptoms culminate in lethargy and withdrawal from the surroundings. The same symptoms are observed in volunteers injected with low doses of LPS. The possibility that the release of cytokines accounts for more subtle changes in cognition and performance has been assessed by Smith *et al.*[43] On the basis of earlier work showing that infection with upper respiratory viruses decreased the efficiency with which psychomotor tasks were performed, volunteers of both sexes were injected with IFNα. Volunteers injected with the larger dose were significantly slower at responding in a reaction time task when they were uncertain when the target stimulus would appear. Simultaneously, they displayed hyperthermia and experienced feelings of illness.

However, they were not impaired on a pursuit tracking task or syntactic reasoning task. These effects were similar to the alterations in performance observed in patients with influenza.[43]

The possibility that proinflammatory cytokines have relatively specific effects on cognitive processes has been further investigated in animal models. IL-1β, but not IL-6, impaired spatial navigation learning in rats.[44] A similar deficit in spatial learning was observed in mice injected with IL-1β or infected with the pathogenic agent *Legionella pneumophila.*[45] Interference of cytokines with formation of new memories has also been demonstrated in an autoshaping task in which rats learned to press a lever that was introduced into the cage before food delivery.[46] These effects of cytokines appear to be independent of their pyrogenic activity since they were observed whether body temperature increased or decreased in response to the treatment under study.

There has been much speculation on the possible pathogenic role of cytokines in chronic fatigue syndrome (CFS). Always feeling tired is a common complaint of patients afflicted with a viral infection and represents the core symptom of the so-called postviral fatigue syndrome. CFS patients feel the same, but in the absence of any persistent viral infection.[47] Their symptoms are real, pervasive, and often incapacitating. The fact that a substantial proportion of these patients fulfill criteria for major depression and other psychiatric illness does not facilitate the classification of this disorder. Whatever the case, and in view of the similarities between the subjective effects of cytokines and the symptoms reported by CFS patients, many researchers have looked for possible overproduction of cytokines in this condition. Elevated plasma levels of proinflammatory cytokines have been reported in a number of studies of CFS patients,[48,49] but these results have not been found in other studies.[50–52] Such inconsistent results can be easily explained by heterogeneity of the clinical population under study, technical problems associated with the detection of cytokines in biological fluids, and the poor correlation between plasma levels of cytokines and local activity of these mediators. A better way of assessing peripheral cytokine function is to study the ability of peripheral blood mononuclear cells (PBMC) to produce cytokines when put in culture and stimulated with adequate stimuli. Using such a strategy, a few authors have found evidence that chronic fatigue is associated with low-level activation of the immune system.[53–55] However, it is important to note that abnormalities, if any, of the cytokine network are not necessarily present at the periphery, but might instead affect preferably cytokines that are expressed in the central nervous system.

Besides their commonality in CFS patients, lack of energy and loss of interest are very frequent in depressed patients. These symptoms are actually incorporated in the basic description of depressive episodes. The tenth revision of the International Classification of Disease begins with the statement that "the subject suffers from a lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration are impaired, and marked tiredness after even minimum effort is common." The possibility that activation of peripheral blood monocytes and T lymphocytes plays a role in the pathophysiology of major depression has been proposed by Maes *et al.*[56] In addition to the evidence pointing out the profound effects of cytokines on behavior and the HPA axis, this hypothesis is based on the observation of an increased production of cytokines by monocytes and T lym-

phocytes of depressed patients. For example, elevated levels of acute phase proteins and increased concentrations of IL-6 and its soluble receptor have been found in the plasma of subjects with major depression and there was a close relationship between IL-6 levels and acute phase proteins. However, more research is still needed before a specific role of immune products in the pathogenesis of depressive symptoms can be accepted.[57] The observed immune alterations appear to be a trait rather than a state marker of depression since they persist even when depressive symptoms regress. Further, the possible contribution of antidepressant treatment to the changes in immune functions observed in depressed patients remains to be established.

If the evidence in favor of an association between depression and an acute phase response is still contradictory, it is clear that administration of cytokines to non-psychiatric patients can induce true depressive episodes. Cytokines are commonly administered in the medical treatment of malignancies and chronic viral infection. The flu-like symptoms that develop very early in all of the patients are followed more or less rapidly by depressed mood and alterations in cognition. Severe depression occurs in about one-third of the patients. Patients treated with IL-2 become clinically depressed after a few days of treatment, whereas patients treated with IFNα become depressed after a few weeks.[58] The risk of developing a depressive episode is positively correlated to the score of depressed mood at the initiation of treatment, despite the fact that the initial scores are within the normal range.[59] There is preliminary evidence that the mood changes induced by IFNα immunotherapy can be prevented by pretreatment with fluoxetine.[60]

The possibility of a role of cytokines in depression has also been studied in animal models of depression. In the absence of any knowledge on the causal factors of depression, most animal models of depression are based on behavioral and pharmacological analogies. At the behavioral level, the two main symptoms that are usually considered include the deficit in escape/avoidance learning and the anhedonia, or more precisely the diminished capacity to experience pleasure, which are typically displayed by experimental animals exposed to uncontrollable electric shocks. At the pharmacological level, chronic (but not acute) treatment with antidepressant drugs blocks the development of these symptoms. A number of studies provide some evidence for a role of cytokines in animal models of depression. Intracerebroventricular administration of the IL-1 receptor antagonist (IL-1ra), which blocks the access of endogenous IL-1 to its receptors, attenuated the escape-avoidance deficit induced by inescapable electric shock in rats.[61] In a different series of experiments, cytokine treatment was found to induce anhedonia in rats, as evidenced by decreased responding for rewarding lateral hypothalamic self-stimulation in response to IL-2 and LPS, but not to IL-1β and IL-6,[62] and attenuated preference for a saccharin solution in response to LPS.[63] This last effect was antagonized by chronic (but not acute) treatment with the antidepressant drug imipramine.[63] The behavioral effects of LPS were attenuated by pretreatment with chronic (but not acute) imipramine.[63] The atypical antidepressant drug tianeptine had the same action. It attenuated the effects of LPS and IL-1β injected peripherally on behavior and pituitary-adrenal activity, but it failed to alter the behavioral effects of LPS and IL-1β when these molecules were injected into the lateral ventricle of the brain.[64]

Since chemical intolerance overlaps considerably with somatization and depression, the possibility that cytokines play a role in the associated symptomatology certainly warrants specific investigations. Positive results were recently reported in

a small-scale study comparing middle-aged women with chemical intolerance to depressed women and a normal control group.[65] Circulating levels of neopterin, a marker of inflammation and monocyte/macrophage activation, did not differ between groups, but were positively correlated with chemical intolerance and somatization scales.

CONCLUSIONS

Sufficient evidence is now available to accept the concept that cytokines are interpreted by the brain as molecular signals of sickness. Sickness can actually be considered as a motivation, that is, a central state that organizes perception and action in face of this particular threat that is represented by infectious pathogens. A sick individual does not have the same priorities as a well one, and this reorganization of priorities is mediated by the effects of cytokines on a number of peripheral and central targets. The elucidation of the mechanisms that are involved in these effects should give new insight on the way that sickness and recovery processes are organized in the brain.

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