

■ H Y P O T H E S I S

Chronic fatigue syndrome: a hypothesis focusing on the autonomic nervous system

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A B S T R A C T

Chronic fatigue syndrome is a debilitating illness of unknown aetiology, with estimated levels of prevalence of up to about 8.7/100 000 in the U.S.A. Like pain fatigue it is a personal, emotionally rich experience, which may originate from peripheral or central sites (or both). The nature of the symptoms is complex and reflects the interaction of the patient with the environment and cultural milieu. Accordingly the common use of the same terminology for different types of fatigue may be misleading. Autonomic activation is a key component of both real and simulated physical exercise. Alterations in autonomic nervous system activity are a key component of several physiopathological conditions. In chronic fatigue syndrome disturbances in autonomic activity, and in other homeostatic mechanisms, such as the hormonal and immune systems, have been reported recently. In this review we followed the hypothesis that in chronic fatigue syndrome the paradoxical condition of disturbing somatic symptoms in the absence of organic evidence of disease might be addressed by focusing on attending functional correlates. In particular we addressed possible alterations in cardiovascular autonomic control, as can be assessed by spectral analysis of R–R interval and systolic arterial pressure variability. With this approach, in subjects complaining of unexplained fatigue, we obtained data suggesting a condition of prevailing sympathetic modulation of the sino-atrial node at rest, and reduced responsiveness to excitatory stimuli. Far from considering the issue resolved, we propose that in the context of the multiple physiological and psychological interactions involved in the perception and self-reporting of *symptoms*, attendant changes in physiological equivalents might furnish a convenient assessment independent from subjective components. Indices of sympathetic modulation could, accordingly, provide quantifiable *signs* of the interaction between subject's efforts and environmental demands, independently of self descriptions, which could provide convenient measurable outcomes, both for diagnosis and treatment titration in chronic fatigue syndrome.

INTRODUCTION

In recent years the active role of patients in chronic, long-standing conditions and in the establishment of preventive strategies has gained attention as a key ingredient of therapeutic approaches integrating pharmacological and behavioural treatments. Accordingly, tailored

strategies aiming to accommodate patients' attitudes and preferences [1] are increasingly being employed in such disparate conditions as hypertension, heart failure, postmenopausal hormone therapy and cancer. Patients' well being and quality of life are part of this novel approach to holistic health care, which assesses clinical outcome [2], focusing not only on the usual objective signs, but also on

Key words: depression, homeostasis, immunology, pain, stress, sympathetic nervous system.

Abbreviations: CFS, chronic fatigue syndrome; HF, high frequency; LF, low frequency; MSNA, muscle sympathetic nerve activity.

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subjective symptoms. There are, however, several problems with this approach. The clinical interpretation of subjective symptoms [3] entails a large margin of uncertainty, in view of the complex, largely elusive link with supportive evidence of organ disorder [4,5]. Symptoms may be present in the absence of any objective sign of illness, as witnessed by the old controversy opposing organic versus non-organic disease [6]. Such a dichotomy may be traced as far back as the Hippocratic writings, which considered diseases as ‘affecting either the structures or the powers of the body’ [7]. More importantly, in the context of the patient–physician relationship, the patient’s focus is on a self-description of the subjective world, usually with the intention to seek medical advice or help; conversely, the physician’s focus is on the patient’s biology, with an intention to treat. Accordingly, the nature of the symptoms is complex, and not limited to patients’ immediate reality, but also reflects the interaction with the environment [8] and cultural milieu. Persistent and, at times, disrupting somatic symptoms are frequently encountered in medical practice, in the absence of any objective sign of disease [9]: it is estimated that up to 40% of those who seek medical advice have medically unexplained somatic symptoms. These symptoms may indicate the presence of an underlying mental disorder (i.e. a ‘disease’ of the patient’s interpretative system), but may also represent a culture-specific way of expressing psychosocial distress (i.e. a ‘language’ difference). In many cultures, somatic symptoms are more common than emotional complaints, as a means to express personal or social distress. For instance, people from Latin cultures are more likely to report somatic symptoms than people from non-Latin cultures. In patients with unexplained symptoms, weakness is frequently present (36%) and often temporally associated with stressful life events. On the other hand, content analysis of medically unexplained somatic symptoms reveals that attribution and interpretation are largely dependent on beliefs and attitudes towards health and disease. Also, the choice of treatment may be largely determined by these factors. The persistence of these complaints and the social pressure for rapid and definitive therapy may lead to overinvestigation, misdiagnosis and unnecessary surgery. The result is an increased burden on medical services, on society and on patients.

These preliminary considerations might help to better focus the ambiguity implicit in chronic fatigue syndrome (CFS), and the mounting role played by the lay press. In addition, self-organized patient initiatives are emerging on the Internet [10], which will surely lead to an increased awareness, as further documented by the existence of a journal specifically dedicated to this syndrome.

Fatigue and chronic fatigue

Fatigue, classically [11] defined as tiredness or weariness, is usually assumed to derive from physical exertion

Table 1 Frequency of concordance of fatigue and other symptoms in the scientific literature

	Fatigue	Chronic fatigue syndrome
Medline 1966 to present		
total no. of papers	5875	1264
Additional symptoms (values per 1000)		
Depression	51	55
Pain	44	14
Stress	32	6
Digestive symptoms	31	5
Sleep disorders	27	25
Muscle disease	19	7
Fever	14	6
Autonomic nervous system	5	2
Sympathetic nervous system	5	2
Emotions	2	2
Inflammation	1	2

(*physical fatigue*), but it may also arise from intense mental work (*mental fatigue*). However, feelings of fatigue may be present without evidence of sufficient expenditure of either physical or mental activity. This type of fatigue, once defined as *emotional fatigue*, initially received attention mostly from psychiatrists, although fatigue is a very common symptom in medical practice. Use of the same term for the physical tiredness after muscular exertion, for the fatigue of mental effort and the weariness of emotional conflicts, as well as for the feeling of weakness or low energy associated with several diseases, is confusing. This nosographic difficulty may have ancient roots. In fact, in Indo-European languages [12], words denoting emotions or feelings originally described the characteristic gestures that are associated with them. Accordingly, expressions for ‘weakness’ or for bodily symptoms thereof, such as ‘droop, pass away, move slowly’, turned into words for related feelings (‘sadness’ and ‘suffering’), that are the general outward sign of the ‘asthenic’ emotions. As an example, *crāmyati*, the Vedic word for ‘take pains, labour’ changed in Classics Sanskrit into *klāmati*, ‘grow weary, weariness’, related to *klāma-* ‘fatigue’, and *klānta*, ‘tired’, whence ‘languid, sad’. In brief, there seems to be a clear historical link between words denoting ‘weakness’ with those denoting the relevant bodily appearance: ‘drooping’ and with expression of negative feelings: ‘sad, dejected’, or loss: ‘sorrow, grief’. A similar path also seems to be present in modern scientific language. Frequency and concordance analysis in peer reviewed papers present in the Medline database show that fatigue is associated particularly with depression, disordered sleep and pain, but also with stress, while muscular disturbance, fever and inflammation rank relatively low (Table 1).

In this article we will affirm the importance of the

complex intertwining of subjective and objective components, looking at the complex mix of symptoms (and language) that are associated with long-standing fatigue of unknown origin, but we will not address acute fatigue arising from obvious sources.

Central and peripheral mechanisms of fatigue

Like pain, fatigue is a personal, emotionally rich experience, which may originate from neural (or chemical) peripheral signals, interpreted centrally, but could also be of central autochthonous origin [13]. Therefore, in the interpretation of fatigue as a symptom, not only the neural integrative properties of the central nervous system, with attendant functional or anatomical integrity, must be considered, but also psychosocial and cognitive aspects must be addressed.

An involvement of central neural structures in the genesis of fatigue is suggested by studies in post-polio sequelae. Post-mortem neurohistopathology and magnetic resonance imaging, showing polioencephalitic damage to the reticular activating system, hint at its involvement in the excessive fatigue (and hyperalgesia) present in post-polio syndrome [14]. However, as in pain, it is likely that cortical structures also participate in the genesis of the subjective experience of fatigue [15].

Fatigue may also originate from peripheral signals. Fatigue as a functional sign of muscle damage can be observed after prolonged exercise [16], usually associated with muscle soreness, particularly if physical activity is intense, and insufficient time is allowed for recovery between each bout of exercise. In addition, altered electromyographic activity, muscle pain and fatigue may follow long-standing mental stress [17].

Weakness, associated with malaise, listlessness and inability to concentrate, together with altered sleep and depressed activity, usually accompany the occurrence of infections. These non-specific changes, collectively called 'sickness behaviour' [18], are interpreted as part of an organized defence response to antigenic challenge, and are thought to be mediated by the neural effects of cytokines. In this context, physiological arousal, aggression and fear are as adaptive as fever, fatigue and rest: in the same way that exaggerated aggressiveness or fear can be detrimental, excessive fatigue can be negative.

Fatigue and sympathetic activity

Autonomic activation is a physiological component of both real and simulated physical exercise [19], as much as fatigue may be the consequence of intense physical activity. Muscular fatigue derives from central factors (i.e. residing in the brain) and from the muscles themselves [13]. Excessive activation of peripheral ergo-reflexes, secondary to muscle dysfunction, is supposed to be responsible for part of the persistent sympathetic

activation of chronic heart failure [20], and abnormal reflex muscle function has also been observed in fatiguing muscle [21]. Although fatigue may be difficult to assess quantitatively, a behavioural scale from no fatigue to unbearable [22] has been used to address its relationship with sympathetic nervous activity, as measured by direct intraneural recordings of muscle sympathetic nerve activity (MSNA) [23]. A clear correlation was found between levels of fatigue sensation and MSNA, during static contraction. Furthermore, exhausting incremental exercise provokes sustained increases of plasma nor-adrenaline, which outlast the termination of exercise by several hours [24]. Similar long-lasting effects of maximal exercise on autonomic activity modulating the sino-atrial node have been reported using spectral analysis of R-R interval variability [25]. Exercise-induced increases in sympathetic activity may be enhanced by simultaneous changes in local humoral milieu, such as those produced by muscle ischaemia, indicating that metaboreflex may be engaged during fatiguing muscular activity in the absence of a sufficient blood supply [26].

Based on these findings, and following the hypothesis that various levels of autonomic activity might be associated with different functional states [27,28], in the rest of this article considering neurological aspects [29] we will follow the hypothesis that (inappropriate) sympathetic overactivity at rest might represent a neural functional correlate of fatigue [30].

SPECTRAL ANALYSIS OF CARDIOVASCULAR VARIABILITY AND AUTONOMIC NERVOUS SYSTEM FUNCTION

Clinical and experimental investigations in the past few decades have elucidated the pivotal role of neural mechanisms, and in particular of sympathetic activity, in several physiopathological conditions, both as promoters, such as in essential hypertension [31], or triggers, such as in sudden coronary death [32]. Furthermore, it has become clear that they could be properly assessed only in the framework of the dynamics of the sympatho-vagal balance [28], which governs the instantaneous performance of the system. Cardiovascular neural regulation is the integrated response to a continuous central and peripheral interaction of inhibitory (vagal) and excitatory (sympathetic) reflexes. In physiological conditions there is a dynamic closed loop interplay of these reflexes with rhythmic haemodynamic oscillations, such as those caused by respiratory and vasomotor activity. Thus, it has been proposed that power spectrum analysis of short-term fluctuations affecting heart period (R-R interval) [33] and arterial pressure may provide indices of neural regulation and, in particular, of the balance between sympathetic and parasympathetic cardiovascular modulation [28].

The issue is complex and agreement regarding both methodology and interpretation is still incomplete [34,35]. A recent Task Force Document [36] proposed standards of techniques and measurements, highlighting similarities rather than differences among various available approaches and laboratories. Using batch analysis, generally a Fast Fourier Transform or an autoregressive approach is employed [28]. Both methods provide numerically similar results, but the autoregressive techniques may have some advantages. This approach is statistically more robust, even in conditions of marginal stationarity, as is usual in cardiovascular time series, and provides automatically, according to statistical criteria [28,33], the number, centre frequency and associated power of oscillatory components. According to the autoregressive approach that we usually employ [28,33], in stationary conditions, R–R variability contains two principal oscillatory components. The component at the respiratory frequency is called high frequency (HF), and that at about 0.1 Hz is called low frequency (LF); in addition, often a variable fraction of power is associated with a pole centred at 0 Hz (or in the region 0.00–0.03 Hz). Its functional significance is still uncertain. A consistent link appears to exist between the predominance of vagal or sympathetic activity and predominance of HF or LF oscillations respectively. This link is best appreciated using normalized units or the LF/HF ratio. The integrated nature of cardiovascular control mechanisms is further documented by the tight correlation with similar LF and HF oscillations present in arterial pressure and in MSNA [37], undergoing parallel changes with pressure-induced moderate alterations in average nerve activity. In addition, similar LF and HF oscillations have been observed in single thalamic neurons [38], and retroviral staining provided direct evidence of interconnections between vagal and sympathetic pathways at a supra-spinal level [39]. Accordingly, this synchrony of rhythms across central and peripheral structures involved in autonomic regulation supports the concept of common central mechanisms governing sympathetic and parasympathetic rhythmic activity [37].

In brief, although rhythms should not be simply equated to neural structures, functional states likely to be accompanied by an increase in sympathetic activity are characterized by a shift of the LF/HF balance in favour of the LF component; the opposite occurs during presumed increases of vagal activity [28]. With this approach, extrapolations should be avoided or used with caution, while the capacity of providing an individual forecasting of different autonomic profiles should be emphasized [40]. Observations obtained in normal subjects must also be contrasted with observations in extreme conditions of disease, where markedly discordant paradigms might be found. As an example, in severe heart failure, an increase in average MSNA is accompanied by

the absence of LF component, both of R–R interval and of MSNA, suggesting an additional disturbance in oscillators [41]. The interpretation of neural mechanisms underlying various spectral components, and in particular of LF oscillations of R–R variability, should be particularly cautious if respiration [42] is not simultaneously recorded. In fact, in conditions of slow breathing, entrainment might introduce an important amplitude distortion of the LF part of the spectrum. Conversely, the non-physiological metronome breathing [43] induces a prevailing HF component in the R–R variability spectrum [28,33]. In addition, a major role might be hypothesized for baroreflex mechanisms [44] in transferring LF oscillations in pressure to R–R variability. However, previous experiments in conscious dogs [33], and more recent studies in humans with a left ventricle assist device [45], do substantiate directly the view that LF oscillations of R–R variability may be observed independently of an involvement of baroreceptor mechanisms.

In the context of this article, it can be argued that as with mental stress, the quantification of the balance of LF and HF rhythms, paralleling sympatho-vagal interaction, could be used to overcome the issue of autoreferencing [46]. The symptom of fatigue, with its confusing mix of subjective and objective components of emotionally charged behaviour, could be conveniently complemented with the assessment of the quantitative relationship between environmental variables and physiological parameters. In doing so, visceral control mechanisms themselves become behaviour, and are thus directly assessable as signs. In this specific aspect, however, the dramatic changes in respiratory patterns produced by conditions with different levels of arousal or relaxation should not be overlooked [33,42,47,48].

ALTERED HOMOEOSTATIC FUNCTIONS AND AETIOLOGY OF CFS

CFS is considered a debilitating illness of unknown aetiology [49]. Estimated levels of prevalence in the U.S.A., obtained from a study in four cities, ranged from 4.0 to 8.7 per 100 000 inhabitants; 85.4% of the identified cases were female, and 97.7% were Caucasian [50]. Adding the U.K. data of up to 2.6% we might arrive at a figure of 1–2%, equivalent to a maximum of about 40 cases on the average general practitioner's list or half to one million cases in the U.K. [51].

A working case definition of CFS was proposed in 1988 [52], by a team of investigators of the Centers for Disease Control and Prevention (CDC). Major criteria were offered, considering duration and severity of the fatigue, and the exclusion of debilitating illnesses, as well as the presence of other symptoms, that would facilitate the diagnosis. Since then, other conferences and studies

have refined the original working definition (e.g. [53–55]). Large clinical databases confirmed the adequacy of the case definition, and verified that patients are clearly distinguishable from healthy subjects or from patients with depression or multiple sclerosis [56]. In addition, changing some of the items in the list of symptoms has been thought capable of improving the accuracy of diagnosis (e.g. excluding muscle weakness, arthralgias and sleep disturbances, and including anorexia and nausea). The relationship between fatigue and sleep is, however, far from defined [57]. In an effort to enhance the robustness of CFS assessment the use of structured interviews has been proposed, at least in selected populations [58]. Finally, biopsychosocial aspects were also considered important [55], although in practice difficult to apply, because of much needed research on the neurobiology of fatigue [59]. Chronic fatigue is lately being addressed furthermore as a by-product of stress [60], particularly at work [61]. A high level of stress was also reported in the 5 years preceding the occurrence of CFS in a case-control study referring to a metropolitan area in the U.S.A. [62]. Overtraining in athletes [63] has also been linked to CFS; in this case a neuroendocrine and autonomic imbalance might also be present [64].

Neuroendocrinology and immunology

A number of disturbances in the fine tuning of control mechanisms have been found in CFS. For instance, attention to the hypothalamic–pituitary–adrenal axis [65] evidenced a mild glucocorticoid deficit [66], and a blunted 5-hydroxytryptamine-mediated activation of this crucial neuroendocrine mechanism [67]. In practice, hormonal determinations could help in better distinguishing depressed patients, who have higher cortisol levels, from patients with CFS, in whom cortisol levels are low [68]. Although far from definitive, our increasing awareness about neuroendocrine disturbances in CFS is being considered as a useful guide to separate it from psychiatric conditions with overlapping symptoms [69].

Recently, immunological alterations have also been reported, suggesting the presence of an autoimmune component in CFS [70]. In approximately 52% of patients with CFS, autoantibodies to the nuclear envelope, mainly nuclear laminins, implied a prominent role for humoral autoimmunity. In addition, the increased frequency of allergic events, low natural-killer-cell activity and low production of certain interleukins in patients with CFS [71], have been linked to a shift from T-helper-1 to T-helper-2 cytokine profile, a dysregulation observable in various chronic human diseases [72]. This hypothesis appears to be further supported by the occurrence of a special case of CFS in Gulf War veterans, who were exposed to multiple T-helper-2-inducing vaccinations [73]. Also, in this particular case, mood changes and stress were tightly linked with

hormonal alterations, confirming the complex intertwining of various control mechanisms.

Autonomic nervous system

Alterations of autonomic functions have recently [74] been reported in patients with CFS: orthostatic tachycardia, coldness of the extremities, hypothermia, episodes of sweating, profound pallor, sluggish papillary responses, constipation and frequent micturition. Accordingly, the feeling of fatigue and exhaustion experienced by patients with CFS has been attributed to their difficulty in maintaining the erect posture. In addition, a predisposition to syncope was documented with prolonged tilt tests in patients with CFS, in which premorbid psychiatric states and cardiovascular deconditioning had been excluded. The presence of disorders of autonomic function provides strong support for the neurobiological [29] hypothesis of CFS, which could be easily tested in larger groups of patients.

Orthostatic intolerance and autonomic nervous system dysfunction

In healthy individuals orthostatic intolerance is experienced because of inappropriate lowering of arterial pressure upon standing either after prolonged bed rest or after a long duration in real or simulated microgravity conditions, leading to cardiovascular deconditioning [75]. In addition, otherwise healthy subjects, usually young females, might occasionally experience unexplained fainting, as a consequence of vasovagal reactions [22]. Finally, patients with pure autonomic failure [76] or multi-system atrophy experience a severe form of orthostatic intolerance. CFS has features in common with a type of chronic orthostatic intolerance that is accompanied by an exaggerated postural tachycardia and an enhanced sympathetic activity [77]. This syndrome may be linked to decreased plasma volume or a peripheral autonomic neuropathy, sparing cardiac innervation [74]. Taken together with the presence of signs of altered autonomic nervous system function in patients with CFS, these similarities suggest a possible role of cardiovascular deconditioning or of post-viral idiopathic autonomic neuropathy, or both. Although there is no therapy for CFS, some suggestions might be offered by treatments effective in autonomic failure, deconditioning and vasovagal syncope [74]. These include volume repletion with increased sodium intake and agents such as fludrocortisone acetate, possibly associated with α -adrenergic agents. In addition, β -adrenergic blockers might be beneficial with vasovagal syncope. Cautious exercise programmes might also be useful.

Signs of disordered autonomic nervous system function in CFS

The demonstration of altered autonomic nervous system function in CFS is relatively new, probably because of

Table 2 Occurrence and severity of self-reported symptoms in a population of patients with unexplained chronic fatigue

Reproduced from [30].

Symptoms (%)	Patients	Severity
Feeling tired	100	+++
Feeling stressed	100	+++
Nervousness	65	+++
Palpitations	20	+
Altered sleep	20	++
Gastrointestinal upset	10	+

recent technical advancements. In fact, both time and frequency domain measures of heart period and arterial pressure variability, at rest or in response to stimuli, disclose autonomic disturbances long before they become clinically manifest. Autonomic function tests [74] suggest that patients with CFS have a reduced vagal and sympathetic responsiveness to standardized laboratory stimuli (paced breathing, standing up), and that these alterations are inversely related to the amount of residual physical activity. Subtle abnormalities in vagal modulation of R-R period have also been observed using the power of the respiratory component (by fast Fourier transform analysis) of R-R variability in CFS patients at rest, during paced breathing [78] and after a walking test [79]. These findings are in agreement with the observation

of a diminished cardiac response to exercise in patients with CFS [80] possibly contributing to the physical fatigability and avoidance of physically demanding tasks [81]. These studies seem to confirm previous observations from our group [30]: we reported in 1994 that subjects with unexplained chronic fatigue presented signs of resting sympathetic overactivity (and reduced vagal modulation). Although subjects were not recruited in order to strictly fulfil the requirements for CFS, all patients complained of mental and physical fatigue (ICD code 306, 780, 785), and were examined for a total period of 5 months. The study period comprised a 4-week stay in hospital and a 3-month post-hospital observation. We reported the simultaneous presence of disturbing subjective symptoms (see Table 2) and a resting imbalance in sympatho-vagal control of the sino-atrial node (Figure 1). We hypothesized that this functional correlate of subjective discomfort might improve the characterization of the clinical complexity of those patients with symptoms of fatigue but no objective evidence of disease. Both patients and controls were also subjected to a standardized mental stress test [47]: the responsiveness (increase in markers of sympathetic drive and reduction in indices of vagal modulation) was more apparent in controls. Similar reductions in cardiac sympathetic responsiveness occur in other diseases, such as arterial hypertension or myocardial infarction [28]. A reduced responsiveness in sympathetic vasomotor modulation was also observed. Although we could not define the role, if any, of mental factors or of personality in the

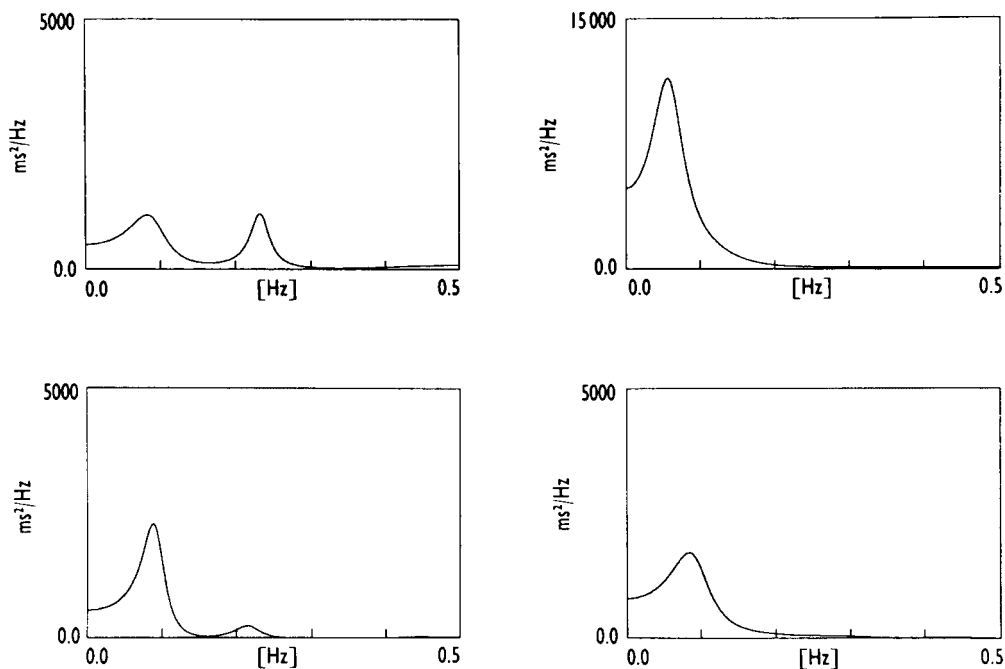


Figure 1 Example of autoregressive spectral analysis of the R-R interval variability during rest conditions (left) and during mental arithmetic (right) in a control subject (top) and in a patient (bottom)

Notice in the auto spectrum of the patient the prevalence, already at rest, of the LF component. Reproduced from [30].

altered sympatho-vagal balance observed in our patient group, we confirmed the reduced responsiveness to stress observed in CFS [29]. We concluded that spectral analysis of cardiovascular variability could be used as a practical way of delving into the complex neurobiology of the CFS, in order to address the physiopathological correlate of a paradoxical condition with subjective symptoms in the absence of physical signs of disease.

CONCLUSIONS

A circular relationship: physical and mental exercise, fatigue and the autonomic nervous system

The term fatigue, used for the physical tiredness following muscular work, as well as for the fatigue of mental effort and the weariness of emotional conflict [10], implicitly assumes a causal relationship with external or internal causes. The same term, fatigue, is also employed when obvious causes are absent, creating a clinical paradox, such as in CFS. Considering the multiple physiological and psychological interactions involved in the perception and self-reporting of symptoms, attendant changes in physiological equivalents might furnish a

convenient assessment independent from subjective components [46]. We had previously explored this approach in the context of the sympathetic overactivity of mental stress [47], which is considered a possible antecedent or cause of CFS. Accordingly, indices of sympathetic modulation could provide quantifiable signs of the interaction between subject's effort and environmental demands, independent of self-descriptions. The schematic illustration of Figure 2 represents an outline of the circular relationship [48] between environment and subject, considering both objective and subjective, i.e. measurable and non-measurable, components of behaviour. The balance between vagal and autonomic neural activities is reflected in the low- and high-frequency rhythms hidden in the R-R variability signal. These oscillations closely track similar rhythms present in efferent sympathetic [37] and vagal nerve activities [28,82]. In brief, recent reports indicating multiple anomalies in various control mechanisms in CFS, including the presence of an autonomic imbalance [30], with sympathetic predominance, could lead to a better understanding of the biology and treatment of this disease condition. Assessing autonomic nervous system function could accordingly help supersede the old controversy between organic and non-organic aspects [30], or the recent conclusion that psychiatry has won the day for now [51]. The quantification of functional disturbances,

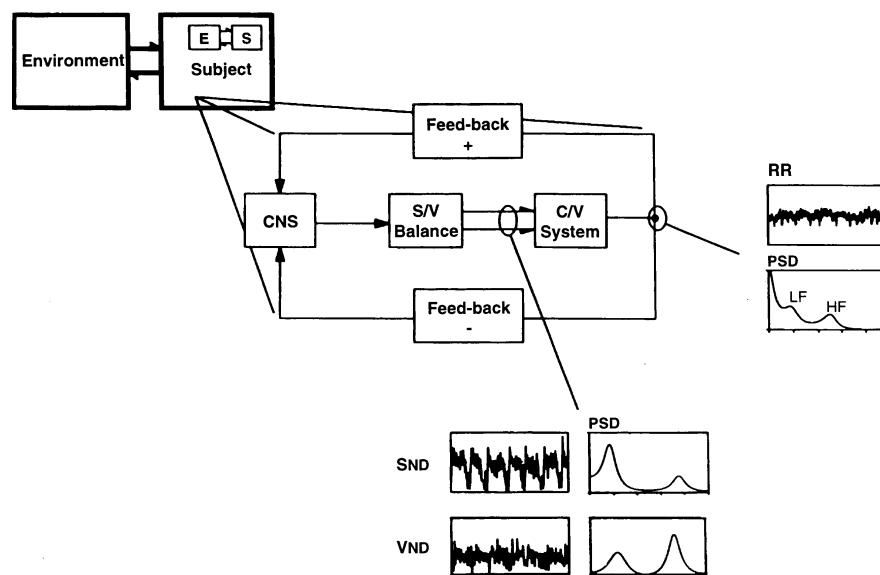


Figure 2 Schematic outline of the circular relationship between environment and subject (top left), as can be used to model the effects of real life stimuli on neural control of the circulation

The presence of a subjective representation of the relationship within the subject is alluded to by the small inset. The blown up schema (centre) refers to the presence of both positive and negative feedback circuits in cardiovascular neural control mechanisms. The continuous dynamic balance between sympathetic and vagal control activities (*S/V balance*) determines beat-by-beat end-organ performance. In both sympathetic (*SND*) and vagal (*VND*) nerve traffic (centre bottom), spectral analysis discloses the presence of simultaneous LF and HF components, paralleling the occurrence of two major similar components in the R-R variability signal (far right), which provide quantitative information on the state of the sympatho-vagal balance. Reproduced from [48] with permission of the publisher, Futura Publishing Company Inc., Armonk, NY.

if corroborated by studies in larger populations, might also provide a convenient way of approaching patients complaining of unexplained fatigue before it becomes severe enough to comply with the criteria for CFS.

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