The aetiopathogenesis of fatigue: unpredictable, complex and persistent

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Abstract

Background: Chronic fatigue syndrome is a common condition characterized by severe fatigue with post-exertional malaise, impaired cognitive ability, poor sleep quality, muscle pain, multi-joint pain, tender lymph nodes, sore throat or headache. Its defining symptom, fatigue is common to several diseases.

Areas of agreement: Research has established a broad picture of impairment across autonomic, endocrine and inflammatory systems though progress seems to have reached an impasse.

Areas of controversy: The absence of a clear consensus view of the pathophysiology of fatigue suggests the need to switch from a focus on abnormalities in one system to an experimental and clinical approach which integrates findings across multiple systems and their constituent parts and to consider multiple environmental factors.

Growing points: We discuss this with reference to three key factors, non-determinism, non-reductionism and self-organization and suggest that an approach based on these principles may afford a coherent explanatory framework for much of the observed phenomena in fatigue and offers promising avenues for future research.

Areas timely for developing research: By adopting this approach, the field can examine issues regarding aetiopathogenesis and treatment, with relevance for future research and clinical practice.

Key words: fatigue, complexity, chronic fatigue syndrome

Introduction

Chronic fatigue syndrome (CFS)[1–6] is a common condition[7,8] characterized by severe fatigue for at least 6 months accompanied by symptoms that include post-exertional malaise, impaired cognitive ability, poor sleep quality, muscle pain, multi-joint pain, tender lymph nodes, sore throat or headache.[5,6,9] Its cardinal symptom, fatigue is commonly experienced in several diseases, it is reported in up to 90% of patients with multiple sclerosis,[1] 90% of patients undergoing treatment for cancer,[2] 98% of patients with rheumatoid arthritis[3] and 93.6% of patients with major depressive disorder.[8,10] The pathophysiology of CFS and of the symptom of fatigue is poorly understood, while several lines of research have now implicated the autonomic, immune and neuroendocrine systems, their causal roles in aetiology are currently unclear and conclusive pathophysiological biomarkers have remained elusive.[11,12] This absence of a clear consensus view of the pathophysiology of fatigue suggests the need to switch from a focus on abnormalities in one system[13,14] to an experimental and clinical approach that integrates findings across multiple systems and their constituent parts and that considers multiple environmental factors. We discuss this with reference to three key factors, non-determinism, non-reductionism and self-organization.

Non-determinism

> '*A philosopher once said, "It is necessary for the very existence of science that the same conditions always produce the same results." Well, they don't!*'—   Richard P. Feynman

Several potential causal factors have been implicated in fatigue and CFS over the past 25 years.[15] These include certain viral pathogens (e.g. the Epstein-Barr virus, XMRV and human herpes virus 6),[16–18] other illnesses (e.g. cancer and rheumatoid arthritis),[19,20] psychosocial adversity (e.g. childhood trauma and occupational stress)[21,22] and factors relating to exercise and nutrition.[23] It should also be noted, however, that sporadic cases of idiopathic fatigue are discussed in the literature.[24] The inconsistency of these findings[25] may suggest that a wide range of potential causal agents can precipitate a common set of symptoms,[26,27] but, critically, the presence of these potential causal agents does not inevitably lead to fatigue. This non-deterministic view is reconciled with current evidence, which shows that specific factors can increase the risk for fatigue but cannot be held as inevitable precursors.[28,29] Therefore, the presence of fatigue does not implicate any particular causal agent or mechanism. In a computational sense, this means that complete information regarding the current state of a system is independent from its initial state, a phenomenon referred to as the Markov property [The Markov property refers to the statistical independence of the current state of a stochastic process from all but its most recent previous states: $P(X_t|X_{(t-1)}) = P(X_t|X_1, \ldots X_{(t-1)})$].[30] In the case of fatigue, this means that for any one patient we cannot say with certainty whether one of the aforementioned aetiological factors is present prior to clinical examination, and for any single experiment we cannot say with certainty prior to measurement what the average score on some aetiologically significant variable might be. We can, however, quantify this uncertainty in the form of probabilities and this (we tentatively hope!) gets to the heart of what is meant by 'risk factors' and 'heterogeneity'.

This entails wider replication of studies and a full appreciation that some experiments will not produce significant results—indeed it is crucial towards establishing precise probability distributions that we acknowledge those studies that do not produce significant findings. Odds ratios can be expressed in Bayesian terms as the ratio of posterior distributions from two groups conditioned on the same evidence and so logistic regression analyses provide useful results, though fully quantifying the conditional probabilities of fatigue given each potential risk factor and their conjunctions is the next step. Bayesian analytic techniques represent a natural solution to this problem by allowing existing beliefs to be updated in light of new evidence. This is in contrast to the less useful, but more widely used, frequentist position which has far less predictive utility. Bayesian approaches also have the pragmatic benefit of greater

flexibility and a reliance on fewer assumptions. Their adoption will therefore allow a much richer appreciation of the heterogeneity of fatigue and may ultimately provide useful guides for targeted preventative interventions.

Of course, this has powerful implications for pathophysiological cross-sectional studies that average across large groups of patients and may thus miss the full nature of this inter-individual variability. By speaking in probabilistic terms, high variability simply corresponds to lower precision in expected beliefs, and thus, variability becomes crucial when reasoning in a probabilistic framework and can be quantified in the precision statistics of probability distributions. These can be tested analytically using basic comparisons of these measures across different demographic groups or can be examined using more advanced statistics based on measures of entropy and cross entropy, as has become standard in bioinformatics and has been used in some studies in patients with CFS with interesting and informative results.[31,32] Therefore, in conducting these studies, while comparing mean scores on various outcome variables, it will be crucial to examine the variability across patients.

Non-determinism is therefore a powerful, but often underappreciated concept in thinking about fatigue-related illness. By embracing this approach, we may appreciate the vast heterogeneity in aetiopathogenesis and, indeed, variability itself in key parameters may emerge as potential markers. Thinking about variability requires a probabilistic (statistical) approach that is characterized by large replication of experiments and may also entail novel inferential methods, particularly Bayesian analysis.

Non-reductionism

'The whole is more than the sum of its parts'—
Aristotle

Fatigue and CFS have been shown to involve several abnormally functioning regulatory systems. The most consistently demonstrated abnormalities lie in the autonomic nervous system, the HPA axis and the immune system.[33–35] Despite this, the identification of diagnostic markers relating to these systems remains elusive,[12] so it is now unclear whether impairment in each system is of central aetiological importance or represents an epiphenomenon associated with a more general causative mechanism. While models have been proposed which combine several factors,[36] they have proved incomplete or difficult to test and generally still adopt a linear approach. We argue that this results from a failure to appreciate the intimate relationships between different subsystems that are crucial to the disease process. The current view is inherently reductionist and assumes that some single factor (or collection of factors) can explain and predict the onset of fatigue.

$$\text{Fatigue} = \alpha + \beta + \gamma + \cdots + \omega \, \text{Health}$$
$$= \beta + \gamma + \cdots + \omega \, \text{Fatigue} - \text{Health} = \alpha$$

This is reflected in several methodological approaches that have attempted to identify biomarkers incorporating blood pressure variability,[37] elevated pro-inflammatory cytokine levels,[38] elevated natural killer cells[39] and certain nucleotide polymorphisms in key neuroendocrine genes (glucocorticoid receptor, NR3C1 and catechol-*o*-methyltransferase)[40,41] but have failed to transfer to clinical diagnosis and have not been replicated in other studies.[25] In essence, the reductionist approaches look for some single factor or collection of factors that is altered in patients compared with controls and posits that these explain (or maybe even are, in a literal sense) fatigue. This is the analytic consequence of assuming that disease states (including health) are the linear summation of constituent parts. As such, though research has identified some key areas of investigation to date, the reductionist approach has hindered further progress.

In contrast, non-reductionism posits that the crucial aspect of fatigue is not the components of these subsystems themselves, but rather the interactions between them. Under this framework, fatigue becomes an emergent property of the system dynamics considered as a whole and the role of intercellular signalling and molecular dynamics becomes crucial.[11] Heuristically, this is a form of biomedical

holism and is encapsulated by the systems approach to biology.[42,43]

$$\text{Fatigue} = \nabla(\alpha + \beta + \gamma + \cdots + \omega)^{\nabla}$$
$$= \left(\frac{\delta}{\delta\alpha} + \frac{\delta}{\delta\beta} + \frac{\delta}{\delta\gamma} + \cdots \frac{\delta}{\delta\omega}\right)$$

This says that rather than focusing on the additive effects of each potential aetiological factor, we must focus on the way in which a change in one variable instantiates a change in the other variables. This has gained significant ground in other aspects of biomedicine, particularly genetics where bioinformatics approaches are becoming standard,[44,45] though has not been adopted by researchers in fatigue, where it is likely to yield substantial gains.

As well as being conceptually parsimonious, this approach makes sense given the evidence that the autonomic nervous system, the immune system and the HPA axis are intimately linked. For example, the anti-inflammatory properties of elevated cortisol have been well demonstrated whereby glucocorticoid receptor activation seems to have a positive effect on anti-inflammatory cytokine production[46] such that, after the induction of stress, a state of Th2 dominance and anti-inflammatory activity occurs.[10,47] Similarly, both systems are influenced by the action of the autonomic nervous system. Noradrenergic projections from the brainstem are present in a variety of immune organs that express beta-adrenergic receptors.[48,49] Noradrenaline innervation therefore inhibits the release of pro-inflammatory cytokines during stress.[50,51] The PNS also has an inhibitory action on the inflammatory response via modulation by acetylcholine.[52,53] It seems clear that alterations in the interaction between these systems may be of crucial importance to the aetiopathogenesis of fatigue and should be the focus for further investigation.

As is clear from the preceding paragraph, in a non-reductionist framework, inter- and intra-system molecular signalling becomes crucial.[54] It is interesting to note that recent evidence has shown catecholaminergic hyporesponse to insulin stress test,[55] heightened HPA axis response to pharmacological challenge[33] and loss of communication among cytokine networks.[56] This provides clear evidence that nature of fatigue and CFS may lie in the efficacy of message passing and inter-cellular communication among diverse ranges of physiological networks. Though unexplored, this also provides a tentative hypothesis explaining the vast array of other disorders in which fatigue is found, as functional/structural change at any point in these networks is capable of inducing global change in output and changing neuropeptide transmission. Indeed, this framework makes searches for specific biomarkers somewhat futile, and more success may be gained through broad characterization of network integrity within systems.

It is important to acknowledge in greater detail that one group has adopted the systems approach in their investigations into fatigue, using information theoretic measures of mutual dependency.[31,32] In particular, one large and elegant study examined the inflammatory milieu in patients with CFS to provide substantial evidence that the mutual information contained with a network of cytokine–cytokine interactions is altered in patients and described by a concentrated hub of Th1 cells.[56] This is despite lowered presence of these cytokines,[57] pointing to alterations in the regulation of the inflammatory system and loss of feedback between the two cell networks. This is a striking demonstration that alterations in the effects of different factors on each other may be crucial in the study of fatigue and similar approaches should be generally adopted. This entails large-scale studies examining several aspects of the autonomic, immune and neuroendocrine systems to gain a complete description of fatigue and its aetiology and treatment. Specifically computational modelling of various regulatory systems and subsequent testing of predictions in larger focused studies is warranted.

Self-organization

'Living matter evades the decay to equilibrium'—
Erwin Schrödinger

In his seminal lecture series, 'What is life?' Schrödinger proposed that biological systems possess the crucial ability to preserve their internal milieu in the face of a constantly changing environment.[58] This is described by a principle of self-organization whereby such systems ensure that they occupy a limited

number of internally consistent environmental states to establish and maintain homeostasis.[59] This self-organizing behaviour is fundamental to the persistence of the system over time and is thought to be achieved by adjusting internal and external states until they reach an equilibrium density of least entropy.[60,61] Interestingly, this principle entails that biological systems are thermodynamically open[62] which heuristically means that they can alter their environment to match their physiological demands or they can change their physiological configuration so it better matches the environment. In practice, this represents the typical negative feedback loops that characterize homeostatic regulators (e.g. cortisol feedback from corticosteroid receptors, the baroreceptor reflex) and ensures the environmental signals received by particular cells are consistent with the set point of a system. This, therefore, allows the system to avoid the decay to equilibrium.

However, if the environment is sufficiently extreme, this is likely to necessitate a change in physiological state (indeed failure to do so is likely to result in serious insult to physiological integrity if not death[63]). The crucial role of a large array of environmental factors in the aetiology of fatigue and the emergence of epigenetics as a key field of research[64] supports this as a crucial consideration. For example, chronic infection is frequently reported by patients as the precipitating factor in their illness and recent epigenome-wide studies have shown hypomethylation in several CpG islands of immunomodulatory genes.[65] Methylation of genes crucial to HPA axis and autonomic tone has been demonstrated in response to environmental challenge across healthy samples and in other illness which, interestingly, includes POTS.[66–68] Given the abundance of evidence that suggests the biological impairment in fatigue crucially involves three homeostatic systems and the interaction with their environment epigenetics is a crucial area for future investigation. It is also important to note that environment refers to any fluctuations outside the system of interest, so the environment for the HPA axis includes signals from the autonomic and immune systems. As such, the principle of self-organization posits that fatigue is the product of biological struggles as internal systems attempt to reconcile their physiological states with their chronic environment. Interestingly, this principle suggests the epigenome and changes to the internal physiological milieu are a pragmatically adaptive response to unpredictable stressors, the consequences of which result in symptom onset.[32]

The capacity for biological systems to regulate their physiological parameters in the face of stochastic environmental fluctuations is crucial but often overlooked. The finding that fatigue appears to crucially depend on function in three of the major homeostatic systems points to a crucial role of the interplay between environment and their physiology.

Discussion

In this article, we have highlighted three basic principles that should inform approaches to research in fatigue and CFS. While they may be implied in some studies and aspects may be acknowledged by the field at large, formal description and their relationship to the evidence in the literature is not only useful, but necessary to further progress. Indeed, we argue that any theoretical approach to fatigue must be able to incorporate these principles.

The regulatory systems that have been implicated in fatigue are subject to random environmental fluctuations throughout their lifetime and thus attempt to enforce stability both by configuring a set point that affords maximum prediction and by changing the internal physiological milieu.[69] This means that physiological output is an expectation value calculated as a function of previous input which itself is a product of the output. There is an inherent circular causality implied in this framework which preserves the self-organizing nature of the systems. By applying this formalism, theoretical accounts of brain function have been developed which describe the brain as a generator of top-down predictions about the likely constituents of sensorimotor and interoceptive data to be challenged against real world perturbations.[70–72] Indeed, a broad array of data now supports this claim.[73] Accordingly brain connectivity at any point encodes a kind of probability distribution over its environment with expectations relating to tonic synaptic drives and precision reflecting the extent of bottom-up message passing or synaptic gain control.[70]

If predictions are violated by unexpected environmental data, synaptic activity can be altered, the environment can be altered to maintain the prediction or precision can be relaxed.[69] Allostasis essentially describes the second phenomenon[69] and requires very precise coding. Such precision is capable of attenuating autonomic reflexes in unpredictable circumstances to return systems to their stable tonic drives.[74]

However, if the environment becomes unpredictable and wildly fluctuates (e.g. in overtraining, childhood trauma, chronic infection, etc.), precision becomes impossible and the corresponding autonomic reflexes are allowed to persist. Of course, if such environmental unpredictability becomes chronic, then precision over sensorimotor/interoceptive data is markedly diminished resulting in heightened autonomic drive. This removes the outdated counterplay between brain input and output and shifts focus to the attempts of the brain to resolve differences between the two. Essentially, what we are proposing is that fatigue results from a computational pathology characterized by a chronic inability to reconcile top-down predictions (i.e. tonic autonomic drives) and bottom-up data (i.e. autonomic reflex arcs). This should manifest as increased sympatho-vagal tone with loss of bottom-up feedback (i.e. loss of baroreflex gain)—the autonomic profile typically seen in fatigue. This places the autonomic nervous system at the heart of fatigue and specifically the failure of regulatory feedback loops to maintain appropriate autonomic tone.

Of course, under the principle of non-reductionism, this loss of precision will result in changes to other regulatory systems due to increased catecholamine signalling. The ensuing dynamics warrant either a change in physiological state or a relaxation in the gain control over ascending feedback loops and the typical HPA axis profile seen in CFS likely reflects the latter which is indicated by loss of circadian rhythmicity and cortisol rate of change.[75] Circadian variations in cortisol are the consequence of exquisite control over adrenal and glucocorticoid receptor sensitivity which is ameliorated with loss of gain control from chronic environmental stress. Indeed, this picture is supported by one recent review showing attenuation in cortisol awakening response as the most consistent abnormality in CFS.[76] Indeed, it may be the case that conclusions regarding basal HPA axis tone are clouded by considering single statistic measures of cortisol throughout the day without attention to circadian variations. Specifically, it may be a useful avenue for future work to explore whether the geometrical pattern of cortisol change over the circadian period is altered in patients relative to controls. Inflammatory markers are likely to be altered in a similar way and characterized by loss of feedback within cytokine networks, exactly in line with Broderick *et al.* (2010).[56] The hypothesis we put forward is that this reflects environmental uncertainty and the amplifying effects on autonomic reflex arcs.

Under this conception, fatigue is a period of prolonged and hyperactive autonomic drive and its effects on other regulatory systems. Chronic fatigue is related to inappropriate loss of reflex feedback control and the detrimental effects of this on immune/endocrine function.

Future work

Given this view of fatigue and CFS, several avenues of potential future work become important. Perhaps most pertinent relates to the proposed variability in physiological profiles that is expected under this formalism and says that searching for a consistent biomarker may prove elusive under a reductionist approach. Instead systems-based research is mandated. In the first instance, this entails mathematical and computational based modelling, using Bayesian techniques,[77] to establish a basic approach to understanding of system integrity which can then be used to examine phenotypes emerging from lesions to different points within these systems or alterations in the neuromodulation. It is expected that similar outcomes will be gained from deletions at numerous points, and so translating this approach to aetiological studies may look for measures of overall system integrity rather than unique parameters. Similarly, variability itself can be quantified, and this may prove useful in understanding the pathogenic process. In translating this, computational approach to basic research imaging techniques now exist which allow an examination of functional connectivity among different brain regions.
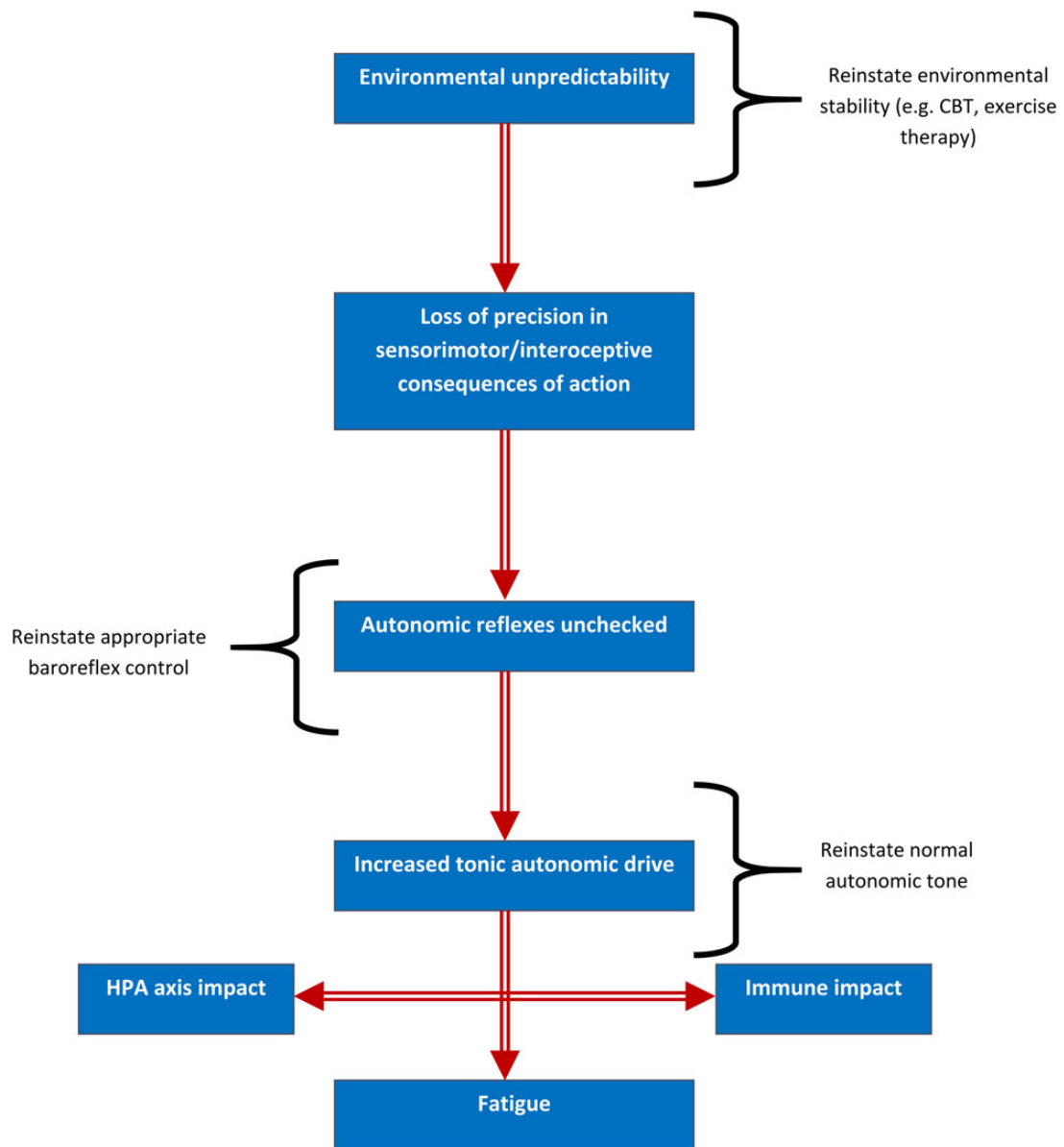
Fig. 1 Model of the aetiopathogenesis of fatigue with treatment options.

We hypothesize that alterations in connectivity will be prominent in fatigue, and this will be a more productive route than analytic techniques driven by the general linear model.

Of course, this new approach suggests various levels at which treatment might be targeted (Fig. 1). The first is reinstating environmental gain control through behaviourally driven intervention, and this may explain the apparent efficacy of cognitive behavioural therapy and graded exercise therapy.[78] In addition, it could be achieved by direct pharmacological reinstatement of autonomic tone or by re-establishing negative feedback loops within the autonomic hierarchy. The fundamental circularity implied by a non-reductionist, self-organizing framework means targeting all three may prove most appealing. Indeed, this

may point to why single pharmacological agents have shown limited success in clinical trials (Box 1).

Conclusion

Fatigue and CFS are heterogeneous, prevalent and disabling, and yet our understanding of a core aetio-pathological process is poor and correspondingly treatment options are currently limited. We have proposed three principles that are mandated by the literature but which have been neglected to date. By motivating an approach based on these principles, we arrive at a coherent explanatory framework for much of the observed phenomena in fatigue that offers promising avenues for future research.

Conflict of interest statement

The authors have no potential conflicts of interest.

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