

Persistent burnout theory of chronic fatigue syndrome

David Jameson

davidj@mind-body-health.net

ABSTRACT

There is no agreement on the etiology of chronic fatigue syndrome (CFS), and the main theories (behavioural and viral/immune) do not satisfactorily explain all findings. A growing body of evidence shows that CFS appears to be a dysfunction of the stress system—and the hypothalamic–pituitary–adrenal (HPA) axis in particular—as a result of chronic stress. CFS shares many similarities to occupational burnout, including similar symptoms, physiological abnormalities and triggers. After a review of the available evidence, I hypothesize that CFS is a state of persistent burnout that remains after the initial stressors have been removed. This persistence may be due to a combination of a dysregulation of the HPA axis and behavioural factors.

Existing theories

Chronic Fatigue Syndrome (CFS) is the internationally accepted term for long-term, disabling fatigue—along with other symptoms such as musculoskeletal pain, sleep disturbances and impaired concentration—which has no known medical cause.¹

There is no generally accepted theory as to what causes CFS. The main theories about the etiology of CFS are the psychiatric (cognitive behavioural) theory, and the viral theory. The cognitive behavioural theory posits that CFS is caused by an initial trigger (such as a virus or stressor), but maintained by behavioural factors such as exercise avoidance and abnormal illness beliefs.² The viral theory posits that CFS is caused either by a so-far-undetected virus, or that the immune system in patients is compromised and allows viruses such as herpesvirus to persist.³

The problem with the cognitive behavioural theory is that it does not adequately explain all of the signs and symptoms of CFS, such as the endocrine and immune irregularities, simply putting these down to mind-body interactions without really trying to explain them. It also does not adequately explain findings about patients' history, personality and pre-morbid lifestyle.⁴ A meta-analysis by Malouff et al. found that including

cognitive elements in a treatment did not lead to a greater effect, and there appears to be no empirical basis for including cognitive components in the treatment of CFS.⁵ Exercise avoidance or deconditioning do not adequately explain findings such as abnormal performance in repeated cardiopulmonary exercise tests.^{6,7} A review by Wiborg et al. found that the effectiveness of CBT was independent of any persistent change in physical activity.⁸ Together these findings suggest that deconditioning, exercise avoidance and cognitive behavioural factors do not satisfactorily explain the etiology of CFS. The cognitive behavioural theory essentially explains CFS symptoms by saying “while your illness might have been triggered by a virus, it is being perpetuated by your beliefs”, which does not really correspond with the experiences of the patients themselves. It is not surprising that there is such a vehement backlash against any psychological explanation for the illness.⁹

The problem with the viral theory is that no single virus has been found in all CFS patients. While high titers of HHV6, EBV and other virus antibodies are commonly found in patients, this is also sometimes found in healthy patients and simply reflects prior infection. Furthermore, some research shows no immune dysfunction in patients at all.¹⁰ It is possible that there is some as-yet-undiscovered virus hiding out in the bodies of CFS patients, but such a theory is not credible until evidence is produced.

Hypothalamic–pituitary–adrenal axis

There are many different CFS symptoms, and no two patients have exactly the same set of symptoms. However there are certain abnormalities that appear to be present in the majority of patients. One common finding is a dysfunction in the hypothalamic–pituitary–adrenal (HPA) axis, including blunted HPA axis responsiveness, mild hypocortisolism, and a lower than normal variation in the normal circadian pattern of HPA axis activation.¹¹ Given that the HPA axis is an important modulator of the immune system, this may explain the immune abnormalities seen in CFS.¹²

Most CFS cases are triggered by either an infectious illness, a stressful life event, or a combination of the two.¹³ Viral infections are physiologically stressful, and they activate the HPA axis in a similar way to psychological stressors.¹⁴

A number of studies have shown that CFS patients tend to have a Th2-type immune response, and this has been shown to be due to increased sensitivity to cortisol. Increased sensitivity to cortisol is typically a result of long-term hypocortisolism, and is thought to be a compensatory mechanism.¹⁵

CFS patients appear to have an “action-prone” (or hyperactive) personality,¹⁶ which then appears to result in a “crash” of the stress system due to excessive chronic stress.¹⁷ The HPA axis dysfunction in CFS appears to be due to enhanced HPA axis negative feedback, which may be mediated by mineralocorticoid and glucocorticoid receptors in the brain.¹¹ Similar enhanced negative feedback is also seen in post-traumatic stress disorder (PTSD), burnout, childhood sexual abuse, adolescents exposed to earthquake-trauma, and chronic pelvic pain.¹⁸

Underactivation of the HPA axis

While stress normally results in an increase in HPA axis activation, chronic long-term stress can paradoxically lead to an underactivation of the HPA axis, hypocortisolism, and fatigue.¹⁹ This was first noted by Hans Selye, who termed it general adaptation syndrome (GAS). The earliest research showed that chronic stress was associated with a reduced daily output of cortisol. However this went against the prevailing dogma that stress was associated with high cortisol output, so the results languished for 10–15 years. Subsequent research has shown that chronic stress can result in both high and low cortisol depending on the nature of the threat, the time since onset, and the person's response to the situation. Cortisol output tends to be elevated initially, and then tends to reduce as time passes. Underactivation of the HPA axis is consistently seen in both PTSD and CFS,^{19,11} as well as after cessation of chronic stress.²⁰

Cortisol awakening response

The cortisol awakening response (CAR) is a measure of cortisol in the 30–60 minutes after waking, and is believed to be a reliable indicator of HPA axis responsiveness. Normally cortisol rises just after waking—similar to a mild stressor—in anticipation of events during the day. During periods of stress, the CAR is elevated, whereas in CFS, chronic pain disorders, functional gastrointestinal disorders and PTSD, it tends to be blunted.²¹ Two studies have shown that the hypocortisolism in CFS is normalised after treatment, and that response to treatment is associated with normalization of cortisol in patients.^{22,23}

Hall et al. found that perceived stress management skills are related to greater CAR response in CFS patients, and a greater CAR results in reduced post-exertional malaise (PEM). The authors hypothesize that higher cortisol may protect against CFS symptoms such as PEM due to its effects on energy metabolism. Alternatively, the hypocortisolism in CFS—and resulting changes in inflammatory cytokines—may result in increased inflammation after exertion.²⁴

Burnout

Burnout is a state of exhaustion due to excessive demands of a job (e.g. workload or time pressure), and insufficient resources (e.g. being in control, or having a variety of tasks). It has been shown that job demands correlate with feelings of exhaustion in burned out workers.²⁵

Research has shown that patients suffering from fatigue, burnout or exhaustion tend to have a reduced CAR compared to controls, whereas job stress and general life stress is associated with an increased CAR.²⁶ When comparing the CAR response of burned-out teachers, Pruessner et al. found that both stress and burnout had independent effects on cortisol secretion (positive for stress and negative for burnout), and they suggest that the HPA axis might be independently affected by stress and burnout.²⁷

Fries et al. hypothesize that the hypocortisolism seen in stress-related disorders is a protective mechanism which has evolved to conserve energy during threats that are beyond the organism's ability to cope.¹²

Persistent burnout theory of chronic fatigue syndrome

Burnout and CFS share similar symptoms, as well as both being triggered by stress.²⁸ The main difference between burnout and CFS appears to be illness attribution: psychological for burnout, and physical for CFS.^{28,29} Both CFS and burnout show a hypofunction of the HPA axis, which appears to resolve in burnout after taking time off work, but persists in CFS.

The persistent burnout theory of CFS proposes that CFS is a state of persistent burnout, which remains after the initial stressors have been removed. The burnout is caused either by cessation of chronic stress, or begins during the period of stress. Persistence is maintained either via changes in the HPA axis resulting in a dysregulation in the stress system,¹⁷ or due to cognitive behavioural factors,² or a combination of both.

Burnout and HPA axis hypoactivation may be a protective mechanism that has evolved to protect the organism from the effects of chronic stress, and CFS may be a maladaptive burnout state that does not resolve after cessation of the stressor.

Further research is needed to elucidate the brain structures responsible for burnout and CFS, but the prefrontal cortex (PFC) may be involved. The PFC is thought to be important in achieving long-term goals,³⁰ and is an important part of the negative feedback regulation of the HPA axis.³¹ A number of studies have shown that CFS patients have reduced grey matter volume in the lateral PFC, and one study has shown that this reduction is reversed after treatment with CBT.³² It may be that in CFS the PFC gets stuck in a negative

feedback loop due to perceived lack of goals and negative outlook, which is reinforced by the resulting symptoms of HPA axis hypoactivation.

Recovery from CFS is difficult, and current treatments such as cognitive behavioural therapy (CBT) and graded exercise therapy (GET) are only moderately effective for treating CFS. The fact that cognitive elements do not appear to make a therapy more effective, and that recovery is not associated with an increase in activity, calls into question the theories behind these treatments. The moderate effectiveness of these (and other) treatments may simply be due to the fact that they give the HPA axis a benign “kick”, reversing the state of persistent hypoactivation. Or perhaps they are simply a placebo that gives the patient self-efficacy and a positive goal to work towards. Simply reducing stress and pacing activities does not generally result in recovery from CFS.³³

Anecdotally, patients seem to use a variety of unproven treatments that sometimes lead to recovery. The only common factors among all these treatments seem to be self-efficacy and the achievement of positive goals. Low self-efficacy has been shown to be a risk factor for both burnout and CFS,^{34,35} and a lack of positive goals has been shown to be a factor in both persistent pain and workplace burnout. Increasing self-efficacy has been shown to reduce fatigue, pain and depression.³⁶

Burnout and CFS appear to be the result of long-term stress combined with a negative perception of the stress. With CFS, the illness itself may lead to continued stress and negative outlook, due to negative feedback, even in the absence of ongoing stressors. Increasing positive goals and self-efficacy is thus a plausible treatment approach.

Future directions

There are still a lot of unknowns about the etiology of CFS. There is some disagreement about the nature of the HPA axis dysfunction between studies. Future measurement of HPA axis and autonomic nervous system parameters in the days before and after exercise challenges may help to elucidate the nature of the HPA axis and autonomic dysfunction in patients, as well as shedding light on the nature of the post-exertional malaise seen in CFS. More effective treatments are desperately needed, and a better understanding of the etiology of the illness will likely lead to this happening.

References

1. Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., & Komaroff, A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of internal medicine*,

121(12), 953-959.

2. Deary, V., Chalder, T., & Sharpe, M. (2007). The cognitive behavioural model of medically unexplained symptoms: a theoretical and empirical review. *Clinical psychology review*, 27(7), 781-797.
3. Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B (2012). Chronic fatigue syndrome, the immune system and viral infection. *Brain, Behavior, and Immunity* 26(1): 24-31.
4. Van Houdenhove, B., Luyten, P., & Kempke, S. (2013). Chronic fatigue syndrome/fibromyalgia: a "stress-adaptation" model. *Fatigue: Biomedicine, Health & Behavior*, 1(3), 137-147.
5. Malouff, J. M., Thorsteinsson, E. B., Rooke, S. E., Bhullar, N., & Schutte, N. S. (2008). Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. *Clinical psychology review*, 28(5), 736-745.
6. Vermeulen RCW, Kurk RM, Visser FC, Sluiter W, Scholte HR (2010). Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. *J Transl Med.* 2010; 8: 93.
7. Keller BA, Pryor LP, Giloteaux L (2014). Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO₂peak indicates functional impairment. *Journal of Translational Medicine*, 12(1), 104.
8. Wiborg, J. F., Knoop, H., Stulemeijer, M., Prins, J. B., & Bleijenberg, G. (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychological medicine*, 40(8), 1281.
9. Hawkes, N. (2011). Dangers of research into chronic fatigue syndrome. *BMJ*, 342, d3780.
10. Natelson, B. H., & Lange, G. (2002). A status report on chronic fatigue syndrome. *Environmental health perspectives*, 110(Suppl 4), 673.
11. Papadopoulos, A. S., & Cleare, A. J. (2012). Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. *Nature Reviews Endocrinology*, 8(1), 22-32.
12. Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): facts and future directions. *International Journal of Psychophysiology*, 72(1), 67-73.

13. Salit, I. E. (1997). Precipitating factors for the chronic fatigue syndrome. *Journal of psychiatric research*, 31(1), 59-65.
14. Silverman, M. N., Pearce, B. D., Biron, C. A., & Miller, A. H. (2005). Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral immunology*, 18(1), 41-78.
15. Rohleder, N., Wolf, J. M., & Kirschbaum, C. (2003). Glucocorticoid sensitivity in humans- interindividual differences and acute stress effects. *Stress: The International Journal on the Biology of Stress*, 6(3), 207-222.
16. Van Houdenhove, B., Neerinckx, E., Onghena, P., Lysens, R., & Vertommen, H. (2001). Premorbid "overactive" lifestyle in chronic fatigue syndrome and fibromyalgia: an etiological factor or proof of good citizenship?. *Journal of Psychosomatic Research*, 51(4), 571-576.
17. Van Houdenhove, B., Eede, F. V. D., & Luyten, P. (2009). Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a crash in the stress system?. *Medical hypotheses*, 72(6), 701-705.
18. Gaab, J., Hüster, D., Peisen, R., Engert, V., Schad, T., Schürmeyer, T. H., & Ehlert, U. (2002). Low-dose dexamethasone suppression test in chronic fatigue syndrome and health. *Psychosomatic Medicine*, 64(2), 311-318.
19. Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological bulletin*, 133(1), 25.
20. Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response 1. *Annu. Rev. Physiol.*, 67, 259-284.
21. Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology*, 30(10), 1010-1016.
22. Nijhof, S. L., Rutten, J. M., Uiterwaal, C. S., Bleijenberg, G., Kimpfen, J. L., & Putte, E. M. (2014). The role of hypocortisolism in chronic fatigue syndrome. *Psychoneuroendocrinology*.
23. Roberts, A. D., Papadopoulos, A. S., Wessely, S., Chalder, T., & Cleare, A. J. (2009). Salivary cortisol output before and after cognitive behavioural therapy for chronic fatigue syndrome. *Journal of Affective Disorders*, 115(1), 280-286.

24. Hall, D. L., Lattie, E. G., Antoni, M. H., Fletcher, M. A., Czaja, S., Perdomo, D., & Klimas, N. G. (2014). Stress management skills, cortisol awakening response, and post-exertional malaise in Chronic Fatigue Syndrome. *Psychoneuroendocrinology*, 49, 26-31.
25. Demerouti, E., Bakker, A. B., Nachreiner, F., & Schaufeli, W. B. (2001). The job demands-resources model of burnout. *Journal of Applied psychology*, 86(3), 499.
26. Chida, Y., & Steptoe, A. (2009). Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. *Biological psychology*, 80(3), 265-278.
27. Pruessner, J. C., Hellhammer, D. H., & Kirschbaum, C. (1999). Burnout, perceived stress, and cortisol responses to awakening. *Psychosomatic medicine*, 61(2), 197-204.
28. Leone, S. S., Wessely, S., Huibers, M. J., Knottnerus, J. A., & Kant, I. (2011). Two sides of the same coin? On the history and phenomenology of chronic fatigue and burnout. *Psychology and Health*, 26(4), 449-464.
29. Huibers, M. J. H., Beurskens, A. J. H. M., Prins, J. B., Kant, I. J., Bazelmans, E., Van Schayck, C. P., ... & Bleijenberg, G. (2003). Fatigue, burnout, and chronic fatigue syndrome among employees on sick leave: do attributions make the difference?. *Occupational and environmental medicine*, 60(suppl 1), i26-i31.
30. Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual review of neuroscience*, 24(1), 167-202.
31. Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends in neurosciences*, 20(2), 78-84.
32. de Lange, F. P., Koers, A., Kalkman, J. S., Bleijenberg, G., Hagoort, P., van Der Meer, J. W., & Toni, I. (2008). Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain*, 131(8), 2172-2180.
33. White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., ... & Sharpe, M. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *The Lancet*, 377(9768), 823-836.
34. Schwarzer, R., & Hallum, S. (2008). Perceived teacher self-efficacy as a predictor of job stress and

burnout: Mediation analyses. *Applied Psychology*, 57(s1), 152-171.

35. Findley, J. C., Kerns, R., Weinberg, L. D., & Rosenberg, R. (1998). Self-efficacy as a psychological moderator of chronic fatigue syndrome. *Journal of Behavioral Medicine*, 21(4), 351-362.

36. Maes, S., & Karoly, P. (2005). Self-Regulation Assessment and Intervention in Physical Health and Illness: A Review. *Applied Psychology*, 54(2), 267-299.