

RESEARCH ARTICLE**Fatigue, Susceptibility to the Common Cold and its Behavioural Effects****Author**

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Abstract

The aim of the present article is to describe bi-directional interactions between fatigue and infection with common cold producing viruses. Over one hundred years ago, researchers started to investigate the association between been fatigue and infection. Studies of psychological risk factors for upper respiratory tract illnesses (URTIs) have been carried out for over fifty years. Early research did not control for exposure and also often relied on self-report rather than clinical and virological assessment. Research on experimentally-induced URTIs has demonstrated that susceptibility to infection is increased by stress. Other research has shown that job insecurity, few social contacts, emotional disposition, early childhood experiences, sleep problems and self-rated health are key risk factors for infection. This article provides an interpretation of these results in terms of chronic fatigue increasing susceptibility to infection. Infection and illness also lead to changes in behaviour. These effects include greater fatigue, impaired attention and slower motor speed. Such effects occur not only when the person has symptoms but in the incubation period, with sub-clinical infections, and after the symptoms have gone. Those with URTIs are also more sensitive to other negative factors such as prolonged work, and this has implications for safety-critical jobs. Ingestion of caffeine, which is an established countermeasure for fatigue, can reduce the behavioural malaise induced by URTIs. Further support for the use of a fatigue framework comes from a secondary analysis of data on real-life colds. Previous research has demonstrated that chronic fatigue leads to greater effects of acute fatigue. The new analysis showed that those with high levels of fatigue prior to developing a cold had larger behavioural impairments when they became ill.

Keywords: Fatigue; Common Cold; Stress; Social Support; Sleep; Alertness; Performance

Introduction

This article aims to provide a common conceptual framework for psychological risk factors for susceptibility to the common cold and the behavioural malaise that accompanies the illness. The key concept is chronic fatigue, and the link between this and infection has a long history. Anecdotal reports of the link between fatigue and infection are described in an Editorial in JAMA in 1910¹. Observations during epidemics of plague and cholera suggested that physical or mental exhaustion made the person more susceptible to disease. Vets also observed that overexertion led to a greater risk of anthrax in horses and cattle. Clinical observations in the latter part of the nineteenth century linked fatigue with many diseases of microbic origin (e.g. typhus, tuberculosis and influenza). In 1890 Charrin & Roger² published their classic animal studies on anthrax infection and physical exhaustion, demonstrating that fatigued rats were more susceptible to infection and more severe illnesses. These results were confirmed by De Sandro³ (1910) using other infecting agents and other species of animals. This research also identified some immunological mechanisms underlying the effects of fatigue. First, the leukopenia (decrease in the number of leukocytes) following virus challenge was greater in the fatigued animals. Second, the subsequent polynucleosis (e.g. increase in

neutrophils) was less intense and persistent in the fatigued animals. The mononucleosis (increase in lymphocytes and monocytes) that followed was also less intense in the fatigued animals. Control animals also exceeded the fatigued animals in terms of the amount of agglutinin (antibodies that cause aggregation of antigens) produced.

Psychological risk factors for susceptibility to upper respiratory tract illnesses

Psychologists have carried out research on psychological risk factors for susceptibility to URTIs for over fifty years. Early research, reviewed by Cohen and Williamson (1991)⁴, was criticised for the use of retrospective or cross-sectional designs, lack of control of exposure to the virus, no clinical observations or virological assays, and poor conceptualisation of psychological constructs used. These issues have subsequently been addressed using experimentally induced URTIs, prospective longitudinal designs, control of a range of possible confounders, and more clearly defined psychological models.

Experimentally induced URTIs: The MRC Common Cold Unit, UK.

Research on experimentally induced URTIs was started at the MRC Common Cold Unit, UK.

Volunteers came to the MRC Common Cold Unit, Salisbury, from all parts of the UK and stayed for ten days. Initially, they were given a medical examination, and blood samples were taken to assess pre-existing antibody levels. They were then placed in quarantine for two days to ensure they had not brought an illness with them. They were then given either a virus or saline placebo in droplets up the nose. Each day they were assessed by the unit clinician, and nasal swabs were taken to allow identification of virus shedding.

About one-third of the volunteers developed clinical colds, another third had subclinical infections, and the rest were uninfected (their immune system had quickly dealt with the virus). Blood samples were taken three weeks later and returned to the unit to assess changes in antibodies. Baseline psychological measures were taken during the quarantine period and then again when some of the volunteers were symptomatic.

The first large scale study⁵ found that those with high-stress scores were at greater risk of developing colds than those with lower levels of stress. These results were due to increased susceptibility to infection rather than a greater risk of becoming symptomatic. The effects of stress did not reflect health-related behaviours, although subsequent analyses⁶ found that smoking increased both infection and illness, and consumption of a small amount of alcohol

on a regular basis reduced the symptom severity, possibly due to the anti-inflammatory action reducing nasal symptoms. Different types of stress influenced either infection or illness. Negative affect and perceived stress increased the likelihood of infection, whereas negative life events led to greater symptom severity⁷.

Closure of the MRC Common Cold Unit

Results from studies of psychosocial factors and experimentally induced URTI have been replicated in research on naturally occurring illnesses⁸ and confirmed with other infectious agents⁹. However, the unit closed in 1990, and the experimental induction of colds was then largely carried out in the USA. A series of trials, the Pittsburgh studies (see Cohen, 2005, for a review¹⁰), continued to examine psychosocial factors and susceptibility to URTIs.

Experimentally induced URTIs: The Pittsburgh Studies

Initial research¹¹ showed that chronic stress was the key risk factor for susceptibility to URTIs. Major risk factors were lack of social support and job insecurity. These effects did not reflect personality or health-related behaviours, although these latter factors had independent effects on the disease outcomes. Other research¹² demonstrated that having fewer social ties was also a risk factor for

susceptibility to infection, and more diverse social networks were associated with greater resistance to upper respiratory illness. A positive emotional style also predicted resistance to URTIs¹³, and dispositional affect moderated the buffering effect of social support on the risk of developing a cold¹⁴. Other research investigated the importance of socioeconomic status¹⁵ and parental separation during childhood¹⁶. As in other areas of public health, low income and parental separation were risk factors for URTIs. Other research focused on sleep¹⁷ and showed that shorter sleep duration led to greater susceptibility to the common cold. Later research suggested that this effect of sleep duration was only observed in those with low socioeconomic status¹⁸. Poor self-rated health (SRH) status was also a risk factor for susceptibility to URTIs¹⁹, which probably reflects the association between SRH and premorbid immune dysfunction.

The Pittsburgh studies also aimed to identify the immunological mechanisms linking psychosocial factors to infection. One line of research showed that shorter CD8CD28- T-cell telomere length was a risk factor for experimentally induced acute upper respiratory infection and illness²⁰. Other research^{21,22} supported the view that interleukin-6 (IL-6) might be the link between psychological factors and the risk of infection. Another study examined the role of neuroendocrine factors

and demonstrated an association between basal cortisol production and the risk of URTI infection²³. This provided support for the chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk model²⁴. This view argues that chronic stress interferes with responding to hormones that turn off the pro-inflammatory cytokines. This increases the response of the immune system, which then over-responds and amplifies the symptoms of the URTI. Chronic stressors increase the glucocorticoid response (GCR), which reduces the sensitivity of the immune system to glucocorticoid hormones that normally suppress the inflammatory response. It has been shown that stress increases GCR, which is a risk factor for getting a cold and leads to the production of more pro-inflammatory cytokines (TNF-alpha, IL-beta and IL-6).

A re-interpretation of psychological factors and the common cold: The role of fatigue

This next section examines whether some of the diverse results linking psychosocial factors to susceptibility to experimentally induced URTIs can be put in a fatigue framework. It is not intended to dispute early findings but rather to re-interpret in a parsimonious way. Most psychosocial concepts have many correlated attributes, and the next section examines whether chronic fatigue scores are correlated with some of the risk factors for URTIs.

Smith²⁵ conducted a large scale prospective study of naturally-occurring URTIs. At baseline, participants (N=457) completed a battery of psychosocial questionnaire, one being the Profile of Fatigue Related Symptoms²⁶, and others which had been shown to be predictors of susceptibility to experimentally-induced URTIS. Fatigue showed the following correlations, all of which were significant:

- Negative Life Events: $r = 0.21$
- Perceived Stress Scale: $r = 0.46$
- Social Support (ISEL total score): $r = -0.21$
- UCLA Loneliness score: $r = 0.29$
- Alert mood: $r = -0.26$
- Hedonic Tone: $r = -0.19$
- Anxiety: $r = -0.13$

Not too surprisingly, a literature search also confirms that short sleep time and poor self-rated health are also positively associated with fatigue. Interestingly, fatigue is also correlated with childhood stress²⁷. Mechanisms linking psychosocial factors and susceptibility to URTIs are also related to fatigue (e.g. high cortisol and fatigue²⁸; IL-6 and fatigue²⁹; and telomere length and fatigue³⁰). The next question is whether chronic fatigue is associated with increased susceptibility to URTIs.

Chronic fatigue and susceptibility to URTIs

Two studies of susceptibility to naturally occurring illnesses support the view that chronic fatigue is associated with increased susceptibility to URTIs. Smith et al.³¹ conducted a prospective diary study of susceptibility to colds and influenza. The participants were patients who had been diagnosed with Chronic Fatigue Syndrome (CFS) and healthy controls. The CFS group reported more illnesses and greater severity of symptoms. Smith and Thomas³² repeated the study and included virological assays to identify the infecting agents. The results confirmed that CFS patients reported more URTIs, and the increased infection rates showed that this was not due to a bias in symptom reporting but reflected greater susceptibility to infection.

The above sections suggest that it is reasonable to interpret previous results linking psychosocial factors to susceptibility to URTIs in terms of chronic fatigue. Another area of research, this time studying the effects of URTIs on the brain and behaviour, also supports this approach and is briefly reviewed in the next section.

Effects of URTIs on Behaviour

Research on stress, fatigue and infection is an area of research on how the brain and behaviour influence the immune system. The relationship between the brain and the immune system is bi-

directional, and the next section is concerned with the effect of URTIs on cognition and mood. Again, much of this has involved initial studies of experimentally induced colds and influenza, with the results being confirmed in later research with naturally occurring URTIs. A detailed review of the results from both types of study is given in Smith³³.

Experimentally-induced URTIs

The early studies demonstrated that URTIs were associated with performance impairments and an increase in negative mood³⁴⁻⁴⁰ (reviewed by Smith⁴¹⁻⁴⁵). Colds and influenza were associated with different profiles of impairment, with colds leading to psychomotor slowing and influenza impairing the performance of attention tasks (where the person did not know where the stimulus would be presented or when to respond). The differences between colds and influenza may also reflect the severity of the illnesses and/or the sample sizes in the different studies. Impairments were observed when the person was symptomatic in the incubation period of the illness, with sub-clinical infections, and after the symptoms were no longer present.

Naturally-occurring URTIs:

The initial aim of studies of naturally occurring URTIs was to replicate effects observed with experimentally induced URTIs. This was

achieved^{46,47}, and some of the studies even used virological techniques to identify the infecting agent^{48,49}. Other studies examined possible cognitive mechanisms for the impairments⁵⁰⁻⁵⁸. The early studies used computer-based cognitive tasks but later research used simulations of real-life activities, such as driving⁵⁹⁻⁶⁰, and the results suggested that driving performance may be impaired when the person has a cold.

The combined effects of having a cold and performing in noise⁶¹, after alcohol⁶², and after a day of work⁶³⁻⁶⁴ showed that having a cold led to a greater impact of risk factors for fatigue. Caffeine is a known countermeasure for fatigue, and the impairments seen when the person has a cold could be reduced by ingestion of caffeine⁶⁵⁻⁶⁶. This led to research investigating the neurotransmitter basis of the cold-induced impairments. Research with naturally occurring colds found that the impairments were reduced by a drug which increased the uptake of central noradrenaline⁶⁷. Other researchers⁶⁸ suggested that the impairments related to having a cold were due to sleep disturbance, but there has been little evidence supporting this view⁶⁹⁻⁷⁰.

Research has also examined the immunological basis for the behavioural effects of URTIs. Research at the MRC Common Cold Unit showed that behavioural effects similar to those when a person has influenza were observed

when volunteers were given an injection of alpha interferon⁷¹⁻⁷². Other research suggests that Il-6 may be associated with the mood changes associated with URTIs⁷³ and possibly the psychomotor slowing⁷⁴.

The above section suggests that the effects of URTIs on performance and mood should be examined in a fatigue framework. One more piece of evidence would strengthen this view, and this requires data on the effects of URTIs in those with high and low chronic fatigue.

Acute fatigue in those with chronic fatigue

Research demonstrates that those with chronic fatigue are more sensitive to acute fatigue⁷⁵. In that study, chronic fatigue was defined by the person having been diagnosed with chronic fatigue syndrome. Acute fatigue was assessed by examining changes with time on task. The new analyses presented in the next section used a sample of university students and sub-divided them into high and low fatigue groups based on PFRS fatigue scores collected at baseline and reflecting the month before that time point. High acute fatigue was defined by having a cold (low acute fatigue was being healthy). The outcome measures were subjective alertness and simple reaction time. Details of the methodology are given in Smith⁵⁷ and can be summarised as follows.

A prospective study was carried out, and 200 university students recruited in early autumn and carried out ratings of alertness, a measure of psychomotor speed and completed the profile of fatigue-related states questionnaire. Participants returned to the laboratory when they developed a cold and repeated the procedure. Those who did not catch a cold in 10 weeks were re-test as healthy controls. One hundred and eighty-seven completed the study (91 male, 96 female; mean age 20.9 years, range 18-30 years). Forty-eight developed colds, and the rest were healthy controls. The sample was subdivided into those with high/low fatigue scores (based on a median split) at baseline. A MANOVA was carried out using percentage change from baseline as the dependent variable and cold and fatigue groups as the independent variable. The results are shown in Table 1. There was a highly significant effect of cold status (Wilks' Lambda = 0.586 $p < 0.001$ partial eta = 0.414) and a significant interaction between cold status and baseline fatigue (Wilks Lambda = 0.927 $p < 0.005$ partial eta squared = 0.073). Those with colds reported lower alertness and had a slower psychomotor response. Those with a cold and high baseline fatigue showed the greatest impairments.

Table 1: The effects of having a cold and fatigue status on the percentage change from baseline for the reaction times and alertness ratings.

	Mean (se) % change reaction time	Mean (se) % change alertness
Cold, low fatigue	9.8 (2.3)	-26.6 (3.6)
Cold, High fatigue	15.5 (2.9)	-40.4 (4.6)
Healthy, low fatigue	3.2 (1.3)	-1.5 (2.0)
Healthy, high fatigue	0.0 (1.8)	8.3 (2.9)

Higher RT scores = greater slowing

Lower alertness = greater drop in alertness

Conclusion

Fatigue provides a good conceptual framework for research on susceptibility to URTIs and their effects on behaviour. This does not imply that research using other approaches is wrong, but rather the current view presents the “big picture”, which may make the area more understandable by non-experts, whereas the more focused approaches, which consider specific psychosocial concepts, provide information on the microstructure of associations. Further research, either with experimentally induced URTIs or large scale epidemiological methods, is now required to test the view presented here. In addition, there

should be more attention to the health implications of chronic fatigue.

It should also be pointed out that these illnesses have a major impact on healthcare costs and cause frequent absenteeism from education and work. It has been shown ⁷⁶ that in the USA the annual cost of lost productivity because of the common cold is over \$25 billion, of which \$16.6 billion is due to productivity loss, \$8 billion to absenteeism, and \$230 million to caregiver absenteeism. Other research⁷⁷⁻⁷⁹ has shown that URTIs lead to presenteeism, with academic and work performance being less efficient than normal.

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