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REVIEW

# Twenty-five years of research on the behavioural malaise associated with influenza and the common cold

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**Summary** Minor illnesses such as the common cold and influenza are frequent and widespread. As well as specific symptoms such as nasal problems and fever, these illnesses are associated with a behavioural malaise. One feature of this malaise is reduced alertness and this has been confirmed using subjective reports and objective measures of performance. Such effects have been obtained with both experimentally induced infections and in studies of naturally occurring illnesses. The mechanisms underlying the effects are unclear but possibly reflect effects of cytokines on the CNS which result in changes in neurotransmitter functioning that lead to reduced alertness. The malaise induced by these illnesses has many real-life consequences and activities such as driving and safety at work may be at risk. These illnesses not only have direct effects on performance and mood but also make the person more sensitive to effects of other negative influences such as noise, alcohol and prolonged work. Countermeasures include ingestion of caffeine and other drugs known to increase alertness.


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## 1. Introduction

Upper respiratory tract illnesses (URTIs) such as the common cold and influenza are frequent and widespread. Psychologists have conducted research on such illnesses for a number of reasons. The first area of research has examined associations between psycho-social factors such as stress and susceptibility to infection and illness (e.g. Cohen and Williamson, 1991; Cohen et al., 1991, 2012; Cohen, 2005). A second area of research has investigated whether influenza during pregnancy is a risk factor for schizophrenia (e.g. Crow, 1996). More recently there has been research on the role of psychosocial factors in awareness of the risk of swine flu and uptake of vaccination (e.g. Rubin et al., 2010). Animal studies have also assessed the interaction between the immune system and neurochemistry (e.g. Dunn, 2006) and between cytokines and sickness behaviour (e.g. Dantzer and Kelley, 2007).

These illnesses have a large impact on healthcare costs and are a major cause of absenteeism from work and education. A review of the area (Bramley et al., 2002) concludes that in the USA the economic cost of lost productivity due to the common cold approaches $25 billion, of which $16.6 billion is attributed to productivity loss, $8 billion absenteeism, and $230 million to caregiver absenteeism. Other research has shown that URTIs impact on academic and work performance (Nichol et al., 2005, 2006; Palmer et al., 2010). In addition, quality of life is reduced by such illnesses and the malaise associated with them has been the subject of research for over 25 years. As well as the specific local (e.g. increased nasal secretion; nasal stuffiness) and systemic (e.g. fever; sore throat) symptoms these illnesses are associated with behavioural problems. Changes in subjective mood, psychomotor speed and cognitive function are often referred to as malaise. The research described in this article aimed to describe the behavioural changes associated with URTIs, elucidate underlying mechanisms, and consider the practical implications of such effects. The aim of the present review is to provide a historical account of research on this topic. The review starts with a summary of some early anecdotal accounts which led to more controlled studies. This is then followed by a review of studies of experimentally induced URTIs. Both of these topics have been reviewed in detail before (Smith, 1990, 1992a) and this research was followed by research examining the effects of naturally occurring illnesses. This later research has not been reviewed before and is the main focus of the present article. No single method of searching the literature reveals the extent of the literature on this topic. The review presented here reflects the unique personal knowledge that the author has gained over the last twenty-five years. Such an article not only provides an immediate knowledge base but will form a foundation for future reviews of the area.

## 2. Case histories of impaired function

An initial article (Tye, 1960) described a number of case histories that suggested a link between influenza and accidents. These case histories were supported by road accident statistics from the 1950s which showed an increase in accidents in years when there was an increased prevalence of influenza. This article also cites cases where performance was impaired even when the person was not symptomatic (during the incubation period of the illness and after the symptoms had gone). This is an important observation in that a person with severe symptoms may go to bed and refrain from normal activities but this is unlikely to be the case prior to or after the illness.

Another early paper (Grant, 1972) describes case histories of post-influenzal effects on the decision making of highly skilled technicians. The primary features of these errors were that they were made by individuals who had been ill with influenza but no longer had the primary symptoms; the errors went unnoticed and the person rejected advisory comments from colleagues; and the errors could not be attributed to poor motivation or general lack of ability. Overall, these results suggested that further research was required on the effects of such illnesses on performance efficiency. In parallel with the reporting of these case studies other

research in the USA examined effects of experimentally induced infections.

## 3. Experimental studies of severe infection

An early review of infection and behaviour (Warm and Alluisi, 1967) stated that ''data concerning the effects of infection on human performance are essentially non-existent''. They were referring to infections that do not cause structural damage to the brain and they went on to examine the impact of severe infections on the performance of individuals and groups (Alluisi et al., 1971, 1973; Thurmond et al., 1971). In one study those who became ill showed an average drop in performance of about 25% and after recovery they were still 15% below the level of the control group.

## 4. Naturally occurring illnesses

The illnesses studied in the above experiments were very severe and in most occupations or in education they would lead to absenteeism. In the case of more minor illnesses, such as the common cold, it is likely that individuals may continue to work or study. One paper (Heazlett and Whaley, 1976) reports the effects of having a cold on the performance of 13 year old pupils. The results showed that having a cold had no effect on reading comprehension but did reduced performance on tasks involving auditory or visual perception. These selective effects of minor illnesses clearly required replication and extension. This was done in a series of studies carried out at the MRC Common Cold Unit, Salisbury, in the late 1980s. The main findings from these studies are described in the following section.

## 5. Research at the Medical Research Council (MRC) common cold unit

The routine of the MRC Common Cold Unit is described in detail elsewhere (Tyrrell and Fielder, 2002). The main features can be briefly summarised as follows. Volunteers aged 18—50 years came to the unit for a 10 day stay, during which they agreed to receive an infecting virus inoculation (all procedures of the Common Cold Unit were approved by the Harrow District Ethical Committee and carried out with the informed consent of the volunteers). On the first day of the trial volunteers were given a medical examination and then put into quarantine (in apartments of 1—3 people) and were isolated from outside contact (apart from the staff of the unit) for the rest of the trial. Baseline measures of mood and performance were collected during this period. Volunteers were given a virus challenge (or saline) on day 4 and about one third of the volunteers developed symptoms between 24 and 96 h later (depending on the virus). Another third developed sub-clinical infections (as indicated by virological assays) and the remainder could not be shown to have the virus present (the ''uninfected'' group). The testing was repeated at a time when those with illnesses were symptomatic. The symptoms were rated by the unit's clinician and objective measures of illness recorded (e.g. nasal secretion weights; sub-lingual temperature).

## 6. Experimentally induced influenza illnesses

Early studies of the behavioural effects of experimentally induced URTIs have been described in a number of publications and are summarised in earlier articles (Smith, 1990, 1992a). If one considers influenza first, the initial study (Smith et al., 1987a) showed that those with an influenza B illness had slower reactions when they did not know exactly when or where the stimulus was going to occur. Other tasks showed no significant effect of influenza although this may have reflected the small sample size. Further research (Smith et al., 1988a) found that those with influenza B illnesses were impaired on a visual search task with a high memory load. This impairment was present to a lesser extent in the incubation period and in those who developed sub-clinical infections. Again, no impairment was seen in tasks involving other functions (e.g. a pegboard task; logical reasoning task and a semantic processing task). Two later studies examined the effects of influenza A illnesses. In the first of these (Smith et al., 1989) influenza led to impaired performance when the person did not know which of two possible locations a target was going to be presented in but had no effect when the location was known. A final study (Smith, 1992b) examined the effects of influenza on resistance to distraction. The results showed that those with influenza were more easily distracted by irrelevant stimuli. Overall, these studies of experimentally induced influenza demonstrated selective effects of the illnesses, with tasks involving unknown target locations, distraction or variable timing of the stimuli showing greatest impairment.

Other studies (Smith et al., 1992a) examined the effects of influenza on mood. The results showed that influenza was associated with a general increase in negative affect. There was little evidence of an effect of sub-clinical infection, although this may have reflected the small sample size. One must now ask what mechanisms underlie such effects. One approach was based on the finding (Smith et al., 1988b, 1991a) that an injection of alpha-interferon mimicked effects seen in influenza.

The next section considers results from studies of experimentally induced colds.

## 7. Experimentally induced colds

Early studies of experimentally induced colds showed that the tasks which were impaired differed from those which were sensitive to effects of influenza. For example, Smith et al. (1989) showed that performance of a tracking task was worse in the colds group whereas detection tasks, which were impaired in those with influenza, were not impaired by the cold. These results were replicated and extended in other research (e.g. Smith et al., 1987b) which showed that tasks involving hand-eye co-ordination and psychomotor speed were impaired in both those with colds and those with sub-clinical infections. Similarly, another study (Smith et al., 1988a) found that the colds group had slower performance on a task involving transferring pegs from a full solitaire set to an empty one as quickly as possible but not a search task, a logical reasoning task or a semantic processing task. Other research (Smith et al., 1990) investigated the

after-effects of having a cold (volunteers were tested a week after the cold symptoms had gone). The results confirmed that the impairments continued into convalescence.

Mood changes were examined in these studies and the results showed that fatigue increased with more severe illnesses and that this fatigue persisted after the primary symptoms of the illness had gone. Overall, these initial studies suggested that people with colds report reduced alertness and show psychomotor slowing. These effects may be present even when the person is asymptomatic. The performance impairments were selective and little evidence was found for effects of having a cold on aspects of memory (episodic memory; working memory; and semantic memory, Smith et al., 1990). The psychomotor slowing, reduced alertness and insensitivity of other tasks appeared to generalise across different cold producing viruses (Rhinoviruses, Corona viruses, and Respiratory Syncytial virus). Other effects, such as those on visual perception (contrast sensitivity and visual discomfort) appeared to be virus specific (Smith et al., 1992b).

In summary, the effects of both influenza and the common cold appeared to be reliable but further research was required to determine whether effects could be observed with naturally occurring illnesses. The illnesses induced at the MRC Common Cold Unit were very mild and it is possible that different effects might occur with more severe episodes. For example, Capuron et al. (1999) studied naval cadets attending the infirmary with flu-like symptoms. The results showed that the ill group performed worse on daily memory tasks. These effects were interpreted in terms of infectious disease disturbing the complex cognitive processes associated with attentional functions. Furthermore, impairments were present in both those with and without fever suggesting that the underlying mechanism is not an increase in body temperature per se. It was also the case that sample sizes in the MRC Common Cold Unit studies were often small (e.g. Smith et al., 1987a, compared 3 volunteers with influenza with 7 uninfected volunteers) and used a small number of tasks (e.g. Smith et al., 1987b, used one task; Smith et al., 1989, used two choice reaction time tasks). It is possible that more extensive impairments may become apparent in studies with more power and assessing a wider range of functions (Savory, 1992; Bucks et al., 2008).

## 8. Naturally occurring URTIs

Studying naturally occurring URTIs can be difficult because of the uncertainty of the infecting agent. In order to address this issue studies were conducted in the 1990s to examine the behavioural effects of naturally occurring colds and influenza. In some of the studies the nature of the infecting agent was identified using virological assays. Other studies relied on symptoms and signs to determine whether influenza or colds were being investigated (influenza being defined by the presence of fever and an increase in temperature; colds being defined by increased nasal secretion and the absence of systemic symptoms and signs).

### 8.1. Influenza B illnesses

Smith et al. (1993b) investigated the effects of influenza B illnesses on mood and performance. In the first study volunteers were initially tested when healthy and those who developed an illness were re-tested when ill and again a month later. Nasal swabs and blood samples were taken to identify infecting agents. Those who remained healthy were re-tested two and three months after recruitment. The results showed that those with influenza B infections had a 38% increase in their reaction times to targets occurring at uncertain times. Similarly, their speed of response in a vigilance task and accuracy of performing a choice reaction time task were impaired. Performance on other tasks (e.g. memory accuracy) was unimpaired. A second study examined the effects of influenza on sustained performance and showed that those with influenza B illnesses showed a 19% increase in their reaction times compared to the healthy controls. These results confirmed those found with experimentally induced influenza.

### 8.2. Effects and after effects of naturally occurring colds

Hall and Smith (1996) found that having a cold was associated with a more negative mood and psychomotor impairment but little effect on other cognitive functions. These results were confirmed by Smith et al. (1999a) in a study which also demonstrated that electrophysiological measures (speed of eye movements) are sensitive to the malaise associated with the common cold. Smith et al. (1998) used virological assays to study the effects of the common cold on mood and performance. Results from two studies showed that having a cold was associated with reduced alertness and psychomotor slowing. Other research has confirmed that memory accuracy is not impaired in individuals with colds (Bucks et al., 2008; Smith, 2012b).

Studies carried out by other research groups have also supported these findings and extended them by showing that having a cold reduces task engagement (Matthews et al., 2001) and memory processing speed (Bucks et al., 2008). In addition, it has been found that older adults with a cold showed much greater effects on memory processing speed than younger adults (Bucks et al., 2008). This is supported by research showing that infection or inflammation may have a greater effect on the aged or diseased brain (Perry et al., 2007; Godbout et al., 2008; Huang et al., 2008). Smith (2012c) has shown that those with a cold reported a more negative mood, showed psychomotor slowing, slower encoding of new information and slower working and semantic memory speed. The mood effects were correlated with symptom severity. In contrast, the effects on cognitive function were not associated with symptoms or mood changes.

Hall and Smith (1996) found that impairments were still observable one week after the symptoms of the cold had gone. Smith et al. (2000) also measured performance one week after cold symptoms had gone (but with no testing when the person was symptomatic). There was little evidence of impairments when the person was symptom free apart from on a simple reaction time task where impairments were still apparent immediately after the symptoms had finished and a week later. This set of results suggests that having a cold may influence the learning phase of a task which then leads to impaired performance when the person is subsequently re-tested when healthy. There is also some evidence that simple reaction time is impaired a week after having had a cold and

it is now desirable to assess the biological mechanisms that underlie this. This result also has practical implications in that individuals may be aware of impairments when they are symptomatic but usually return to normal activities when they are symptom free.

### 8.3. Combined effects of URTIs and noise, alcohol, prolonged work and stress

Research has shown that individuals with a cold are more sensitive to noise than healthy individuals. (Smith et al., 1993a). Similarly, Smith et al. (2004) demonstrated that the effects of having a cold (reduced alertness and slower simple reaction time) became greater with prolonged work over the course of the day. Research has also examined the effects of a low dose of alcohol (1.5 ml of vodka per kg body weight) on the mood and performance of healthy volunteers and those with URTIs (Smith et al., 1995). This dose of alcohol had no significant effects on the healthy volunteers. However, those with URTIs reported greater negative mood after alcohol than placebo. The combination of being ill and alcohol also led to a large increase (42%) in choice reaction time. Finally, Smith (submitted) has investigated whether volunteers with a cold who also reported negative life events or frequent daily hassles have greater impairments than the low stress colds group or healthy volunteers. The results showed that the stressed colds group had the slowest reaction times. Overall, the results of these studies show that URTIs not only have a direct effect on behaviour but can also make the person more sensitive to other factors. This means that safe levels based on studies of healthy volunteers may not be appropriate for those with URTIs.

The next section considers findings from studies of simulated driving.

### 8.4. The common cold and simulated driving

A study of simulated driving (Smith, 2006) found that those with a cold hit the kerb more frequently and responded more slowly to unexpected events than healthy volunteers. These findings have been confirmed in a study using a more realistic driving task (Smith and Jamson, 2012). In addition, this last study demonstrated that drivers with a cold drove too close to the car in front and were less able to detect collisions. This provides support for conclusions about URTIs and driving based on case studies. Given that having a minor illness also makes one more susceptible to other risk factors known to impair driving ability (e.g. alcohol; fatigue due to prolonged work) one might expect even greater effects of these illnesses on driving safety. Further research is required to address this last issue.

One must now consider some possible underlying mechanisms for these effects. The initial small scale studies suggested that the mood changes associated with the URTIs were correlated with symptom severity. In contrast, the performance changes were independent of both symptoms and mood changes. Several possible types of mechanism have been put forward to account for the performance changes and the major ones are briefly described below.

## 9. Underlying mechanisms

### 9.1. Effects of cytokines on brain neurochemistry

Unlike many other viruses that affect the brain and behaviour upper respiratory tract viruses are not thought to enter the CNS. The performance effects do not reflect the symptoms of the illness and a more likely mechanism is that they are due to effects of immunological changes on the brain. Cytokine production is viewed as a key element in the host's acute phase reaction to infection (Kraneveld et al., 2008). A number of behavioural symptoms accompany the acute phase reaction and collectively these are known as sickness behaviour (Hart, 1998; Dantzer, 2004). There is substantial evidence for a central role of pro-inflammatory cytokines in the aetiology of these symptoms (see Dantzer and Kelley, 2007). Cognitive decline in older adults has been shown to be associated with elevated levels of plasma IL-6 (Alley et al., 2008). Similarly, there is some evidence from experimentally induced elevations of proinflammatory cytokines that aspects of memory may be related to levels of TNF and IL-6 (Cohen et al., 2003; Krabbe et al., 2005). These findings are supported by animal studies (see Kennedy et al., 2012, for a review) which demonstrate that a number of different proinflammatory cytokines are associated with cognitive impairments. It has been suggested that the relative contribution of cytokines and other inflammatory mediators induced by URTIs on effects on cognition and mood is not well understood and thus needs assessment (Eccles, 2005). However, human studies using other paradigms (e.g. LPS challenge studies) support the view that central cytokines may be linked to sickness, mood alterations and psychomotor slowing in humans (Brydon et al., 2008; Harrison et al., 2009a,b; Mahoney and Ball, 2002; Vollmer-Conna et al., 2004).

This mechanism appears plausible because of animal research on the effects of cytokines and infections on brain neurochemistry (Dunn, 2006) and cytokine-induced sickness behaviour (Dantzer and Kelley, 2007). Animal research has also investigated changes in memory and LPS inflammatory challenge. For example, Min et al. (2009) demonstrated that LPS challenge produces deficits in spatial memory. Similarly, inflammation has been shown to impair place learning using the contextual fear conditioning paradigm (Pugh et al., 1998; Kranjac et al., 2012). Tanaka et al. (2006) also found that LPS administration into the hippocampus activated microglial cells which decreased glutamatergic transmission and led to deficits in learning and memory. Overall, these results suggest that memory deficits induced by cytokines and other inflammatory mediators are mediated by alteration in the functioning of the hippocampus and cortex.

### 9.2. Stimulation of the trigeminal nerve

One study (Smith et al., 1991b) found that sucking zinc gluconate lozenges and using a nasal spray containing nedocromil sodium removed the cold-induced performance impairment. One way in which these two compounds could produce similar effects is through changes in afferent stimulation. URTIs influence the trigeminal nerve and compounds which increase afferent stimulation may produce changes in

the brain stem. Indeed, the presence of menthol and similar compounds in cold medication is because they produce symptomatic relief by stimulating the trigeminal nerve.

### 9.3. Disturbed sleep

Research (Drake et al., 2000) has examined the effects of experimentally induced rhinovirus infections on sleep. They found that in those with a cold total sleep time decreased by 23 min and sleep efficiency decreased by 5%. Psychomotor performance was also impaired in those with a cold although there was no increase in daytime sleepiness in that group. In addition, there were no significant correlations between changes in sleep parameters and the measures of fatigue. Data on subjective estimations of sleep length and quality suggested that different viral infections have slightly different effects during the incubation period, with influenza infections reducing, and rhinovirus infections increasing, sleep duration. Both illnesses, however, increased sleep on the days when symptoms were observable (Smith, 1991). Smith (2012a) found significant correlations between nasal symptoms and sleep disturbance. Reported fatigue the next day was also associated with less efficient sleep. These results confirm that the common cold can have detrimental effects on sleep but suggest that the overall magnitude of the effect is small and that it may reflect nasal obstruction. The next section considers changes in neurochemistry that may underlie the behavioural effects of URTIs.

### 9.4. Neurotransmitters and malaise

The starting point for this line of research was a study which showed that caffeine removed many of the impairments induced by URTIs (Smith et al., 1997). This led to a study examining whether increases in the turnover of central noradrenaline (produced by the drug idazoxan) could remove the impairments seen in those with a cold (Smith et al., 1999b). The results showed that compounds that increase central noradrenaline may remove the reduced alertness and psychomotor slowing associated with URTIs. It is also quite likely that changes in other neurotransmitter systems are also involved in the malaise associated with URTIs which suggests future pharmacological methods of preventing and removing such effects.

## 10. Conclusions and future directions

This review has shown that URTIs are associated with a malaise that includes mood changes and impairments of aspects of mental performance. These illnesses also make the person more sensitive to the negative effects of other factors (e.g. prolonged work, alcohol, and stress). The mechanisms underlying such effects can be considered at many different levels and while our knowledge of these is incomplete, evidence for cytokine changes, reduction in the turnover of central noradrenaline, trigeminal effects and indirect effects of sleep disturbance have been demonstrated. The malaise induced by these illnesses has implications for real-life performance and safety (e.g. impaired driving). Further research is still required to increase our knowledge of the behavioural effects of URTIs so that we gain a better understanding of the underlying mechanisms and the implications for policy and practice.

Further research is required on the effects of prevention and treatment on malaise. In the case of influenza, it is important to evaluate the impact of vaccination. First, vaccination may not only reduce the incidence of significant clinical illness but it may lead to a decrease in other negative outcomes associated with influenza (e.g. absenteeism). However, vaccination can also induce malaise and it is important to monitor the extent and consequences of this. It is also important to develop and evaluate medications that not only treat the local symptoms but remove the behavioural problems produced by the illness. Mahoney and Ball (2002) suggested that there is a need for studies evaluating the efficacy of systemic interventions that target inflammatory mediators, including effects of non-steroidal anti-inflammatory mediators, on malaise. The addition of caffeine to many over-the-counter products may be one method of doing this. Future studies must also test the view that treatment of symptoms may actually increase behavioural problems by interfering with the adaptive responses designed to promote recuperation and recovery from infection (Eccles, 2005).

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I declare that I have no conflict of interest.

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