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Respiratory virus infections and performance

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Minor illnesses, such as colds and influenza, are frequent, widespread and a major cause of absenteeism from work and education. Yet the clinical symptoms of such illnesses may not be so great as to stop people from working or from carrying out everyday activities. It is therefore important to determine whether these viral infections alter central nervous system function and change performance efficiency. Data on this topic are almost non-existent, which in part reflects the difficulties inherent in carrying out such studies. In real life it is almost impossible to predict when such illnesses will occur, and difficult to establish which virus produced the illness.

This problem was overcome by studying experimentally induced infections and illnesses at the Medical Research Centre (MRC) Common Cold Unit in Salisbury. Results from this research programme show that:

(i) colds and influenza have selective effects on performance;
(ii) even sub-clinical infections can produce performance impairments;
(iii) performance may be impaired during the incubation period of the illness;
(iv) performance impairments may still be observed after the clinical symptoms have gone.

These results have strong implications for occupational safety and efficiency and it is now essential to assess the impact of naturally occurring colds and influenza on real-life activities.

1. Introduction

It is widely accepted that the physiological state of the person is very important in determining performance efficiency. This has usually been studied by manipulating some feature of the environment, such as the noise level, or by examining endogenous variations in alertness, or by changing the state of the person by administering drugs. Such studies have usually been carried out with normal, healthy subjects. However, a person's state is frequently changed by infection and illness and it is important to determine whether performance is altered by these. Many illnesses are so severe that the individual is unable to carry out normal activities, and the question of impaired performance does not arise (although the absence of an individual may pose additional problems for other workers). Other illnesses, such as the common cold and influenza, may not be so severe that they prevent a person from working or carrying out other activities. It is important, therefore, to assess the effects that these respiratory virus infections have on performance efficiency.

Respiratory virus illnesses are a major health problem in that the acute infections and their consequences account for a substantial proportion of all consultations in general practice. These illnesses are also one of the main causes of absence from work and education and we spend over one hundred million pounds a year on medication for them. Colds and influenza affect most of the population (it has been estimated that we have between one and three colds a year) and it is highly desirable to increase our knowledge of these illnesses, with the practical aims of lowering health care costs, decreasing absenteeism from work and improving the quality of life.

Despite the frequency with which such illnesses occur there has been no research on their behavioural effects. This is true of infectious diseases in general and Warm & Alluisi (1967) concluded that 'Data concerning the effects of infection on human performance are essentially non-existent'. Since that review the effects of certain infectious diseases have been studied (Alluisi *et al.* 1971, 1973; Thurmond *et al.* 1971). In one experiment (Alluisi *et al.* 1971) volunteers were infected with *Pasteurella tularensis* (which produces rabbit fever, a febrile disease characterized by headache, photophobia, nausea, myalgia and depression). 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. There was also evidence that some types of activity were more impaired than others, with active tasks such as arithmetic computation showing a greater decrement than passive tasks such as watchkeeping. The illnesses studied in these experiments are very severe and analogous effects must rarely occur in everyday life. In contrast to this, colds and influenza are frequent and widespread and yet we have little information on whether they reduce the efficiency of performance.

One possible reason for this lack of research is that people feel they already know about the behavioural effects of such illnesses and it is, therefore, a waste of time carrying out experiments on this topic. One commonly held view is that when someone is ill everything is performed less efficiently than normal. An opposite view is based on the observation that people often go to work when suffering from these illnesses, which suggests that any effects are likely to be too slight or transitory to be of practical importance. An alternative view emerges from the literature on stress and performance. Recent research on the effects of changes in state has shown that different activation states produce distinct profiles of performance changes (see Hockey & Hamilton 1983). Colds and influenza are different in that colds produce local symptoms (nasal secretion) whereas influenza also gives rise to systemic effects. One might, therefore, predict that the two types of illness will change performance in different ways.

Another reason why there has been little research in this area is that it is difficult to study naturally occurring illnesses. These illnesses are hard to predict and it is often unclear which virus is the infecting agent (there are over 200 viruses that produce colds). The study of such illnesses only enables one to examine the effects of clinical illnesses, and it is often difficult to obtain objective measures of the symptoms. It is also possible that sub-clinical infections may influence behaviour and these can only be identified by using the appropriate virological techniques. These problems were overcome here by examining the effects of experimentally induced colds and influenza at the Medical Research Centre (MRC) Common Cold Unit, Salisbury. The main features of the methodology and routine of the Common Cold Unit are summarized in the following section.

2. The routine of the common cold unit

The volunteers, who are aged 18–50 years, come to the unit for a 10-day stay, during which time they agree to receive an infecting virus inoculum. The volunteers are housed in groups of two or three and isolated from outside contacts. Before the visit the volunteers supply the unit with a self-reported medical history. People taking sleeping pills, tranquillisers or anti-depressant medicines are not allowed to take part in the trial, and neither are pregnant women.

On the first day of the visit they undergo a medical examination, and any who fail this are excluded from the trial. A blood sample is also taken at this time to enable assessment of initial antibody level. Isolation begins in the afternoon of the first day and the volunteers are observed during a three-day quarantine period so that any individuals who are incubating a cold may be excluded. A nasal washing is obtained on the third day of the trial and individuals with sub-clinical infections are also excluded.

Volunteers are usually given the virus or saline placebo on the fourth day. The trials are conducted double-blind with neither the volunteers, the unit's clinician nor any of the personnel who interact with the subjects knowing which volunteers received virus or placebo. Volunteers are usually administered 10–100 TCD50 of a rhinovirus by nasal drops. The most common serotypes used are RV9 and RV14, and sometimes both are given. Coronaviruses and respiratory syncytial viruses are used in other trials. Influenza trials are carried out less frequently, but there have been studies of influenza A and influenza B viruses.

Following virus challenge there is an incubation period of 24–96 h depending on the type of virus. In general, about one third of the volunteers develop significant symptoms and one-third have sub-clinical infections. Very few volunteers are given placebo because one third of those given the virus remain uninfected.

On each day of the trial the severity of cold or influenza symptoms is assessed by the unit's clinician. Self-reported respiratory symptoms are also collected on a standardized paper and pencil instrument. Objective measures of symptomatology are also recorded, namely the number of paper handkerchiefs used, the weight of nasal secretion, and sub-lingual temperatures. At the end of the trial the clinician decides whether volunteers have had significant colds or not (according to well-established procedures, see Beare & Reed (1977)). Nasal washings are taken so that the shedding of the virus can be assessed, and a blood sample is returned to the unit three weeks after the visit to allow the antibody level to be measured again.

All procedures of the unit are approved by the Harrow District Ethical Committee and carried out with the true consent of the volunteers.

3. Performance testing

The data reported in this article were collected during clinical trials that had other specific aims. This imposed certain limitations on the type of task and frequency of testing. Similarly, portable tests had to be used because the volunteers were in isolation and could only be tested in their flats.

Two main methods have been used. The first involved administration of paper and pencil tests measuring logical reasoning, visual search and semantic processing at four times of day on every day of the trial. It was important to examine performance at several times of day for two reasons. First, it has been shown that performance changes over the day (see Colquhoun 1971), and secondly, there is diurnal variation in the severity of symptoms of colds and influenza (see Smith *et al.* 1988*a*), with nasal secretion and temperature being greatest in the early morning.

The second method of assessing performance used computerized performance tasks, with volunteers being tested once in the pre-challenge quarantine period and once when symptoms were apparent in some volunteers. In certain trials performance testing was also carried out in the incubation period. Subjects were always tested at the same time of day on all occasions (although some subjects were tested in the morning and others in the afternoon, which meant that diurnal variation could be examined). The computerized tasks were selected to assess a

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range of functions (memory, attention and motor skills) and most of the tests have been widely used in studies of stressors or drugs.

Analyses of covariance have been carried out on the data using the pre-challenge scores as covariates. This statistical technique takes account of baseline differences when assessing the effects of the illness.

4. Early results

Smith *et al.* (1987*a*) compared the effects of colds and influenza on different aspects of psychomotor performance. Two of the tests required subjects to detect and respond quickly to targets appearing at irregular intervals (a variable fore-period simple reaction time task and a 'fives' detection task). The other was a pursuit tracking task designed to test hand–eye coordination.

Influenza B illnesses increased reaction times in both detection tasks. These results are shown in table 1. Analysis of the tracking task showed no significant difference between those with influenza and those who remained healthy.

Table 1. Mean reaction time (milliseconds) in the simple reaction time and fives detection tasks for the influenza and uninfected groups

	influenza	uninfected
simple reaction time task		
pre-challenge	320	348
post-challenge	503	325
fives detection task		
pre-challenge	460	421
post-challenge	573	409

The effects of colds on the three tasks are shown in table 2. The difference between the volunteers with colds and the uninfected subjects was not significant for either detection task. However, volunteers with colds were much worse at the tracking task than those who remained well.

Table 2. Mean scores for volunteers with colds and uninfected subjects on the three performance tasks

(Figures given for simple and fives tasks are in milliseconds.)

	colds	uninfected
simple reaction time task		
pre-challenge	332	329
post-challenge	326	308
fives detection task		
pre-challenge	399	402
post-challenge	392	398
tracking task (number of contacts)		
pre-challenge	13.8	13.3
post-challenge	12.6	21.5

These results show that there are effects of respiratory virus illnesses on performance, but that the functions affected depend on the nature of the illness. Many types of behaviour involve both

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hand–eye coordination and the ability to quickly detect unexpected stimuli. Such tasks may be susceptible to the effects of both colds and influenza. It should be pointed out that the effects of these illnesses were very large. For example, influenza led to a 57% impairment on the reaction time task and a moderate dose of alcohol or having to perform at night would typically produce a 5–10% impairment. The results are of theoretical interest because of the dissociation of functions by the different illnesses. Possible mechanisms underlying these effects are discussed in a later section.

Smith *et al.* (1988*b*) compared the effects of colds and influenza on performance of the paper and pencil tests at four times of day. The main results may be briefly summarized as follows. Influenza B illnesses impaired performance on a visual search task with a high-memory load (subjects had to search for the presence of any of five target letters at the start of a line and the speed and accuracy of searching a 12-line block was recorded). This effect is shown in table 3.

Table 3. Mean times (seconds) to complete the pegboard and search and memory tasks for volunteers challenged with an influenza B virus

(Scores are the adjusted means from analyses of covariance.)

	pegboard	search and memory
uninfected	39.4 s	94.8
sub-clinical infection	45.0	108.3
influenza	42.6	135.8

In contrast to this, volunteers with influenza were not impaired on a test of manual dexterity and movement time (the subject had to transfer pegs as quickly as possible from one pocket solitaire set to another). Volunteers who developed colds after challenge with respiratory syncytial virus were impaired on the pegboard task but not on the search task. The pegboard data are shown in figure 1. Neither influenza nor colds impaired the speed or accuracy of logical reasoning nor semantic processing.

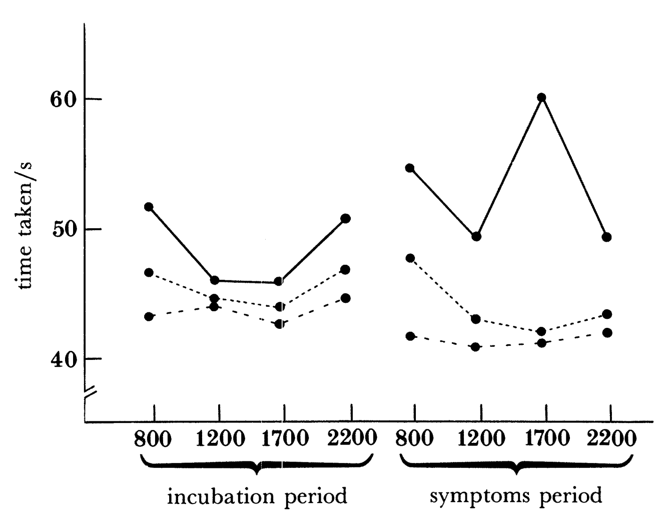

Figure 1. Effects of colds on performance of the pegboard task at four times of day during the incubation and symptoms period. (——), clinical group; (----), sub-clinical group; (–––) uninfected group. (Times are the adjusted means from analyses of covariance.)

5. Sub-clinical infections

One of the great advantages of studying experimentally induced respiratory infections is that it is possible to examine the effects of sub-clinical infections. Table 3 shows that those volunteers with sub-clinical influenza B infections were slower on the five-item search task than those who remained uninfected. This effect of sub-clinical infection was not observed in the colds–pegboard data. However, results from another experiment suggest that sub-clinical infections with cold-producing viruses can also impair performance. This experiment (Smith *et al.* 1987 *b*) examined the effects of colds and sub-clinical infections on performance of the five-choice serial response task. The subject was shown five boxes in a row across the computer screen and when a black square appeared in a box the subject had to press the corresponding key on the computer keyboard. As soon as the subject responded the square reappeared and the subject had to make the next response. The results are shown in table 4, and it can be seen that both those volunteers with significant colds and those with sub-clinical infections were slower than the uninfected group.

Table 4. Mean number of responses per minute in the five-choice serial reaction time task on symptomatic days

(Scores are the adjusted means from analyses of covariance.)

	colds	sub-clinical infection	uninfected
symptomatic days	78.4	78.8	81.6

6. Performance changes during the incubation period

Another advantage of doing this research at the Common Cold Unit is that one knows when the virus was given and one can, therefore, examine changes during the incubation period. Results from the incubation period of the influenza B study showed that behavioural changes precede the onset of clinical symptoms, and the data from the five-item search task are shown in table 5. These results confirm findings from studies of other illnesses (see, for example, Elsass & Henriksen 1984), and suggest that performance changes may be used as indicators of subsequent illness which could certainly be of some practical value.

Table 5. Mean times to complete the search and memory task in the incubation period after challenge with influenza B virus

(Times (seconds) are the adjusted means from an analysis of covariance.)

uninfected	sub-clinical infection	influenza
106.4 s	122.2	144.4

7. After-effects of colds

The fact that sub-clinical infections impair performance and that changes are observed in the incubation period shows that viral infections may alter performance in the absence of clinical symptoms. This issue was also examined by measuring the after-effects of colds on performance

(Smith *et al.* 1990*a*). In this trial volunteers stayed at the unit for three weeks and it was possible to test them not only when they were symptomatic but also one week after the symptoms had gone. The volunteers carried out choice reaction time tasks and those with colds were slower than those without symptoms (see table 6), and this difference was still present one week later, even though the clinical symptoms had gone (see table 6).

Table 6. Effects and after-effects of colds on choice reaction time (milliseconds) performance

	colds	no colds
day 2, pre-challenge	511	523
day 7, symptoms present	530	500
day 14, symptoms no longer present	511	487

These results confirm the findings of Alluisi *et al.* (1971) in showing that effects of viral illnesses continue into convalescence. Grant (1972) has also reported similar after-effects of naturally occurring influenza illnesses. At the moment it is unclear why one gets after-effects of these illnesses. One possibility is that the performance tests are sensitive to the immunological changes that occur after the symptoms have gone. Another possibility is that it represents a carry-over effect, with subjects continuing to perform in the same way as when they were symptomatic. Further experiments are required to resolve this issue.

8. Mechanisms underlying the effects of respiratory virus infections on performance

In influenza, interferon alpha can be found in the circulation and it is now clear that such peptide mediators have effects on the CNS. It was, therefore, postulated that the changes in performance observed in volunteers with influenza may be due to the effect of interferon on the CNS. This was tested by injecting volunteers with different doses of interferon alpha and it was predicted that those who received a dose which produced influenza-like symptoms would show comparable performance impairments. The results are described in detail in Smith *et al.* (1988*c*) and they showed that an interferon injection of 1.5 Mu produced an identical profile of performance changes to those seen in influenza. The smaller doses produced no significant clinical symptoms. Reaction times on the variable fore-period simple reaction time task were slower for the group with clinical symptoms, whereas the other groups improved over the day. This is shown in figure 2. However, neither the tracking task nor logical reasoning task showed any impairment, which confirms negative results obtained in influenza trials.

While interferon-induced changes in CNS function provide a plausible explanation for the selective effects of influenza on performance, it is less clear which mechanisms underlie the effects of colds. One possibility is that some other lymphokine or cytokine, such as interleukin 1, is involved. Indeed, it has been shown that this mediator has an effect on the muscles which could account for the impaired hand–eye coordination. Alternatively, the impairments could reflect changes in sensory stimulation via the trigeminal nerves in the nose.

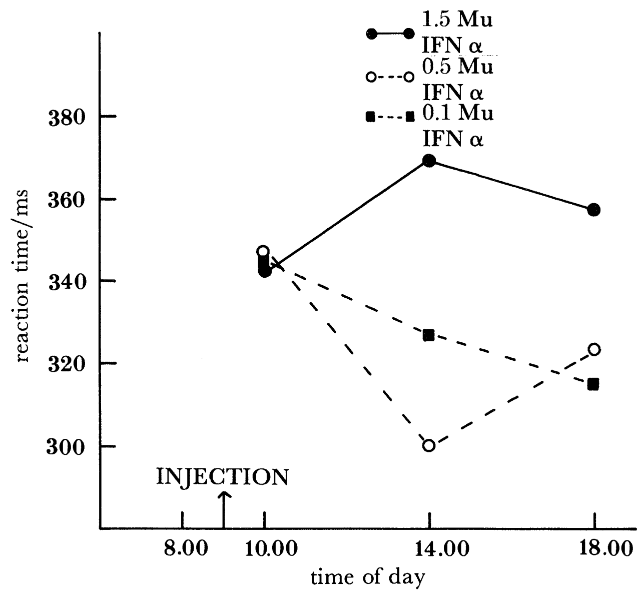

FIGURE 2. Effects of three doses of α-interferon on performance of the variable fore-period reaction time task. (Times are the adjusted means from an analysis of covariance.)

9. RECENT RESULTS

(a) *Colds and memory*

Most of the early studies used simple psychomotor tasks. In recent trials we have examined the effects of colds on different aspects of memory. Many aspects of memory, such as the ability to recall a list of words, or to recall a string of digits in order, appear to be unaffected by having a cold. Colds do appear to impair the learning and recall of more complex material such as stories, and further studies examining the effects of colds on tasks requiring sustained attention are needed. However, colds do not interfere with recall of material learned prior to infection, and there is some evidence that reminiscence, the ability to subsequently recall information which was not retrievable immediately after learning, is better when the person has a cold. This may reflect the decreased arousal produced by the cold, and other conditions that further reduce arousal, such as the consumption of a large lunch, amplify this effect.

(b) *Prediction of susceptibility to illness*

Previous research (see, for example, Totman *et al.* 1980; Broadbent *et al.* 1984) has shown that psychological factors are important in determining susceptibility to infection and illness. For example, introverts appear to be more likely to become infected than extraverts. Our research has shown that measures of performance taken before virus challenge are often related to the probability of developing a cold (see Smith *et al.* 1990*b*). In a very recent study we have examined the relation between visual sensitivity and susceptibility to colds. The volunteers were shown a visually stressful pattern (see Nulty *et al.* 1987) and asked to note the illusions it induced. The results showed that subjects who subsequently developed a cold were more sensitive than those who remained symptom free (see table 7). Furthermore, this test is not related to personality traits such as extraversion or neuroticism, and we have, therefore, a relation between the state of the individual and susceptibility to colds.

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Table 7. Mean number of pre-challenge visual illusions reported by volunteers who subsequently developed colds and those who remained symptom free

significant colds	doubtful colds	no colds
3.2	2.5	1.5

(c) *Drugs, colds and performance*

Many trials at the Common Cold Unit are designed to assess prophylactic and therapeutic drugs. It is possible to assess not only whether the drug modifies the clinical symptoms but also if it removes the performance impairments associated with a cold. One study has examined whether sodium nedocromil (a drug thought to suppress mediators such as histamine) reduces cold symptoms and influences the extent of the cold-induced performance impairment (see Barrow *et al.* 1990). The results showed that volunteers taking nedocromil had less severe colds and that the drug also reduced the size of the cold-induced performance impairment. Unfortunately, the mode of action of nedocromil is unclear and this study provides little further information on the mechanisms underlying the effects of colds on performance.

10. Conclusions

The research described here has demonstrated that experimentally induced upper respiratory virus infections and illnesses can reduce performance efficiency. The exact effect depends on the activity being performed and the type of virus, with colds producing different effects from influenza. The performance impairments are not confined to volunteers with clinical symptoms. Sub-clinical infections can also reduce performance, although once again these effects are selective. Performance also changes in the incubation period before the emergence of the symptoms and the impairments may persist after the symptoms have gone. We have also found that performance measures taken before virus challenge are related to the susceptibility of developing a cold.

While these studies of experimentally induced colds and influenza show that performance is impaired, we have little information on the role played by naturally occurring infections and illnesses in human error. Such illnesses are typically more severe than those we have examined at the Common Cold Unit and one could argue that they should produce far greater effects. However, many workers are well-practised at their jobs and one could suggest that this will make them less susceptible to the effects of these illnesses. The worker is often exposed to a range of factors which may alter performance efficiency and it is possible that viral illnesses may not only have direct effects on performance, but may indirectly influence it by making the person more susceptible to other factors.

Overall, one may conclude that we now have plenty important information about the effects of upper respiratory virus infections on performance efficiency. These results have strong implications for occupational safety and efficiency, and show that it is now essential to assess the real impact of naturally occurring colds and influenza on real-life activities.

I express my gratitude to all the volunteers who have taken part in these experiments, to the Director and Staff of the Common Cold Unit for their help in the clinical trials, and to Kieran

Coyle, Susan Leekam and Len Armer, who have played major roles in the data collection and analysis of experiments.

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