Psychoneuroimmunology, stress and the common cold

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Introduction

Psychoneuroimmunology is the discipline concerned with the study of relationships between behaviour, the brain and the immune system. Links between the central nervous system and the immune system are bi-directional[1]. The brain is involved in the regulation of immune function through autonomic and neuroendocrine pathways, including the sympathoadrenal system and the hypothalamic–pituitary–adrenocortical axis[2]. In turn, immune products, such as cytokines, influence central function and modulate the biobehavioural response to infection and inflammation[3].

There is considerable interest in the clinical implications of psychoneuroimmunology. In this paper, we discuss the possible role of psychoneuroimmunological processes in relation to susceptibility to the common cold, and describe recent studies of psychosocial influences on the acquisition and duration of colds. There is an extensive literature on behavioural stress and infection in animals[4,5], but discussion will be limited to research on humans.

'Stress' as discussed here defines the state that arises when the psychological challenge of external events taxes or exceeds the individual's capacity to adapt[6]. It is a multidimensional state, involving responses at the cognitive, affective, behavioural and biological levels. The events that can elicit stress responses include acute negative life events, chronically adverse circumstances and day-to-day minor irritants or 'hassles'. The factors that influence adaptive capacity include psychological coping responses, social

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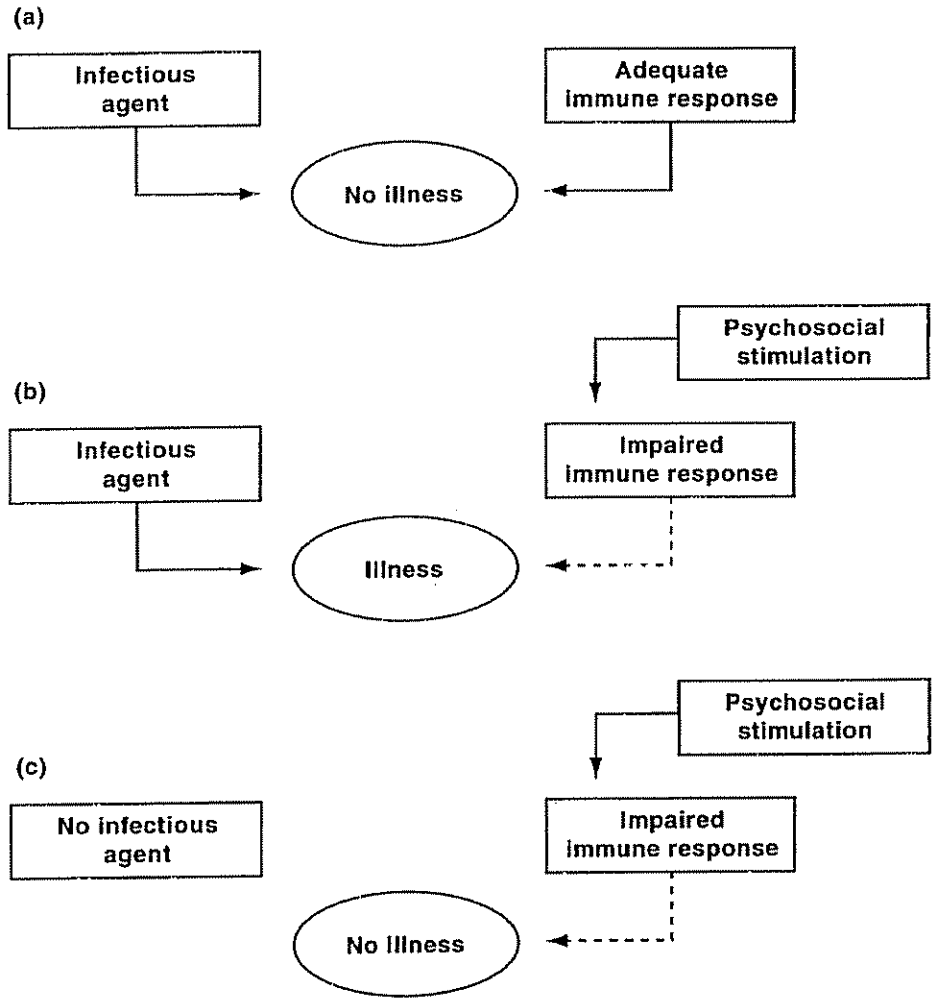

Figure 1

The way in which stress-induced inhibition of immune defences might increase susceptibility to colds. (a) Normal process of effective immune defence; (b) exposure to the infectious agent while immune function is impaired due to psychosocial stimulation; (c) although the immune response is impaired by stress there is no exposure to a pathogen

networks and supports, temperament, prior experience of similar events and genetic disposition[7].

Psychosocial factors and immune responses

The evidence that stress affects immune responses has been reviewed extensively elsewhere[8,9] In response to acute challenges, such as the performance of problem-solving tasks or simulated public speaking, the typical immune responses include an increase in the

number of circulating cytotoxic CD8 and natural killer lymphocytes, together with inhibition of lymphocyte proliferative responses to mitogens[10,11]. Changes in natural killer (NK) cell activity are variable, as increased cytotoxic activity has been reported in some studies and inhibition in others. These responses are transient, returning to baseline levels in about 1 hour of the termination of stimulation. There is convincing evidence that immune responses to acute stress are mediated by sympathoadrenal pathways. The magnitude of responses correlates with sympathetically mediated cardiovascular reactions[10] and acute immune changes are attenuated by β-adrenergic blockade[12,13]. Acute stress-induced immune responses are not associated with cortisol, so the adrenocortical axis does not appear to be involved in their regulation.

Studies of immune function under 'real life' naturalistic conditions have assessed responses to stressful experiences, such as caring for demented relatives, bereavement and marital breakdown leading to separation and divorce. The most consistent responses have been an inhibition of mitogen-induced lymphocyte proliferation and an up-regulation of NK cell cytotoxicity[14]. Clinical depression and low levels of social support are associated with a similar pattern of immune responses. Changes in the numbers and proportions of circulating T-cell subsets have also been described. It has been reported that antigen-specific salivary immunoglobulin A (IgA) production is suppressed when people experience day-to-day minor stressful events[15]. Although the pathways have not been fully elucidated, it is likely that both the adrenocortical axis (via cortisol) and sympathoadrenal system (through direct innervation of lymphatic tissue and the action of circulating catecholamines) are involved. Different pathways therefore appear to mediate acute and chronic stress-induced immune responses.

Functional significance

Critics of research in this area have argued that changes in immune activity resulting from psychosocial stimulation are small, clinically insignificant and in the range of natural variation. It has also been pointed out that immune behaviour is affected by a range of factors, such as smoking, nutrition, minor illness and alcohol consumption, and that it is difficult to rule out these influences in naturalistic studies.

The issue of functional significance has been addressed in a variety of ways in recent research. One approach is to assess antibody responses to latent viruses that remain quiescent in the host unless deficits in immune control allow replication. An elevation in antibody production indicates that viral replication has increased. Several studies have shown that antibody titres to latent herpesviruses, such as herpes simplex, or Epstein–Barr virus are raised as part of the stress response[16,17]. A second method of evaluating functional significance is to assess the

development of immunity following vaccination, on the grounds that antibody production in response to non-pathogenic antigens may be impaired by psychosocial factors. Results of such studies to date have been inconsistent[18], but there is some evidence for impaired antibody production to hepatitis B vaccination in people experiencing psychological stress in their lives[19]. A third method that shows great potential relates to wound healing. Cellular immunity plays an important role in the healing process as cytokines, such as interleukin-1 and tumour necrosis factor, help to protect against infection and repair damaged tissue. Kiecolt-Glaser *et al*[20] made a standard small wound on the forearms of a group of elderly caregivers looking after people with Alzheimer's disease and a group of matched controls, all of whom gave informed consent. Wound healing over the next four weeks was delayed among the caregivers and cytokine responses were impaired. A similar study involving a standard wound to the palates of volunteer dental students showed that wound healing was delayed in the period immediately surrounding an important academic examination in comparison with a control period[21].

The clinical significance of psychoneuroimmunological processes still needs to be convincingly demonstrated for many medical conditions. However, a case can be made for a role in the regulation of malignant tumour growth[22]. Andersen *et al*[23] recently reported that the level of psychological stress assessed with a standardized questionnaire in a cohort of surgically treated patients with breast cancer was correlated with impaired NK cell cytotoxic activity and diminished NK cell responses to cytokines. Stress-induced alterations in immune activity may also affect the development and progression of autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus[24]. Minor stressors are correlated with fluctuations in T- and B-cell counts in patients with rheumatoid arthritis[25], while cognitive–behavioural stress management has been shown to reduce pain intensity, inflammation and rheumatoid factor levels[26]. However, perhaps the clearest evidence for the clinical significance of links between psychological experience and immunology is found the case of infectious illness.

Psychological stress and infection

Many of the effects of psychological stress described in the previous section involve impairment of immune function. The question of whether or not changes in resistance to stress are sufficient to increase vulnerability to infection therefore arises. There are three hypothetical associations between stress factors, immune deficits and infection (Figure 1). In the normal process of effective immune response (Figure 1a), the individual mounts an adequate immune response that tackles the infection and prevents illness. In another scenario (Figure 1b), exposure to the infectious agent takes place against a backdrop of impaired

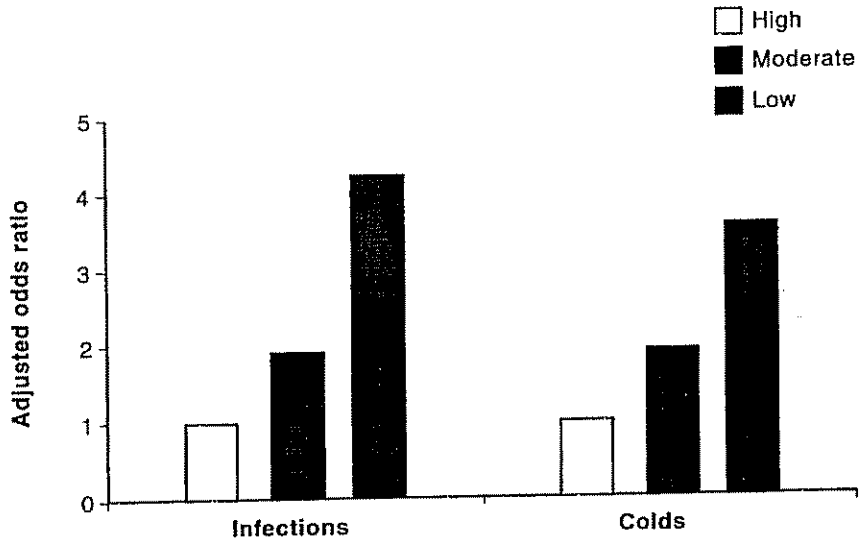

Figure 2

Associations between the extent of social network diversity (high, moderate, or low) and susceptibility to experimentally administered cold virus. Odds ratios (adjusted for potential confounders) for objectively verified infection (left) and symptomatic colds (right) are shown[34]

immune function due to psychosocial stimulation that is insufficient to prevent illness from developing. In a third situation (Figure 1c), stress impairs immune responses but as there is no simultaneous exposure to a pathogen no illness results. This is one reason why some naturalistic studies of psychosocial factors find no effects of stress on infectious illness rates

If psychoneuroimmunological processes are operative, it can be predicted that an individual under stress (Figure 1b) will be more vulnerable to infection than one who is not experiencing stress (Figure 1a). Unfortunately, tests of this hypothesis are complicated by several factors. First, an alteration in immune function is not the only change that takes place with psychological stress. Many people alter their patterns of sleep, eating, physical activity, smoking and alcohol consumption during periods of intense psychological demand[27]. All these factors may, in turn, affect susceptibility to infection, leading to changes in vulnerability independent of psychoneuroimmunological pathways. Second, exposure to infectious agents may be altered by psychosocial factors. One common behavioural response to distressing events is to seek social support and mobilize social networks. Greater social interaction may lead to increased exposure to infectious agents. Alternatively, people may respond to stress by

social withdrawal, thereby reducing their exposure to pathogens. A third problem concerns differences in symptom recognition and reporting. People vary substantially in the extent to which they attend to physical sensations and recognize them as symptoms of illness. One person will struggle into work despite symptoms while another will retire to bed under similar circumstances. The tendency to report illness, self-medicate or seek professional care is associated with chronic stressors, such as excessive workload[28], with variations in subjective distress or negative affect[29] and with individual differences in concern about somatic sensations[30]. The result is that self-reported symptoms may be poor guides to objective infection[31]. These factors may all compromise the study of the impact of psychological stress on the acquisition and duration of infectious illness.

Many of these methodological difficulties can be overcome by studying responses to the experimental administration of common cold viruses. This approach has been developed by Cohen and his colleagues, and we will describe some results from this programme of research on the influence of stress on the susceptibility to infection.

Experimental studies of stress and colds

The experimental administration of cold viruses under controlled conditions provides the most convincing evidence for the influence of psychosocial factors on the susceptibility to infection. In studies of this kind the quantity and timing of infection can be measured precisely, while such information is rarely available in naturalistic settings. Volunteers' social activities are limited by quarantine, and health-related behaviours, such as smoking and alcohol consumption, are controlled. Objective verification of infection and illness is possible through regular physical examinations and viral culture of nasal secretions. All these factors serve to eliminate alternative explanations of findings.

Cohen *et al*[32] investigated the susceptibility to five cold viruses in 394 healthy adult volunteers in their first study carried out at the Medical Research Council Common Cold Unit at Salisbury. A psychological stress index was created through an amalgam of measures of major life events that occurred over the 12 months before the study, scores on the Perceived Stress Scale (a standardized measure of stressful experience) and a measure of negative affect. It was found that the likelihood of infection and illness was positively associated with the psychological stress index, independent of serological status for the experimental virus, age, sex, education, allergic status, season of the year and other risk factors. A 'dose–response' association between psychological stress and illness rates was observed. Changes in health behaviours (smoking, alcohol consumption, physical activity, sleep and diet) did not account for the pattern of responses. White blood cell counts and immunoglobulin levels were not

associated with the stress effect. The influence of stress was equivalent across all five viruses, indicating that the mechanism was not related to the mode of action of any single virus.

A subsequent analysis explored the involvement of the different elements of the psychological stress index[33]. It emerged that the likelihood of infection (as measured by viral culture) was positively associated with high scores on the perceived stress and negative affect scales, but not with high scores of life events. Instead, life events determined whether or not the infected individual went on to develop a clinically verified cold. This suggests that potentially stressful experiences, such as life events, do not increase susceptibility to infection unless they lead to perceptions of distress and lowered mood.

The impact of social factors was examined in another prospective viral challenge study carried out in Pittsburgh[34]. A total of 276 healthy adult volunteers were quarantined and then infected with one of two rhinoviruses. Symptoms, mucus production and cold symptoms were assessed over the following five days. This study also included measures of social networks: participants were asked about their contact with people in several different relationships to them (eg parents, other family members and members of social groups), from which an index of social network diversity was calculated. The sample was subsequently divided into those with high, moderate and low scores on this index, respectively. The results are summarized in Figure 2. After adjustment for eight control variables (age, sex, body mass index, race, season of the year, virus type, education and pre-challenge antibody titres to the specific virus), the likelihood of infection and illness was significantly greater in individuals with limited social networks than in the other participants. Thus, having extensive and diverse social contacts was protective against experimentally administered cold viruses. The probability of infection was also associated with cigarette smoking, low vitamin C intake, low alcohol consumption, lack of regular physical exercise and high levels of urinary noradrenaline and adrenaline. However, these factors did not account for the social network effects.

Further insight into the type of potentially stressful experience that increases vulnerability emerged from a detailed interview carried out with volunteers[35]. The Life Events and Difficulties Schedule developed by George Brown was administered, and participants' experiences over the year before the study were divided into acute stressful events (lasting for less than one month) and chronic stressors. It was found that the risk of developing a cold was not associated with acute events but with chronic stressors, with problems at work and in personal relationships being particularly important. These associations were independent of the social network findings, and again could not be accounted for by differences in health behaviour.

Studies of artificially administered cold virus have been carried out by other investigators, who have found similar effects[36]. These results suggest that a range of psychosocial factors,

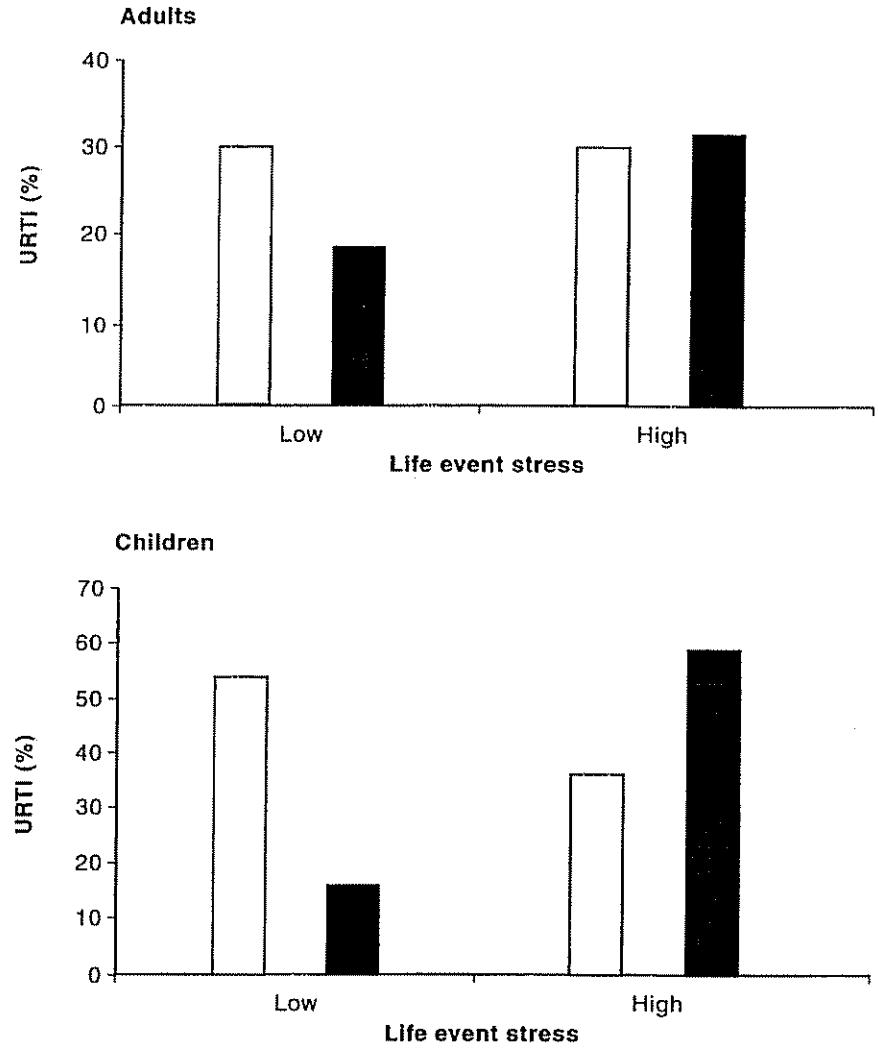

Figure 3

Associations between life event stress and susceptibility to upper respiratory tract infection (URTI) in adults (top) and children (bottom). Participants are divided into those with high (black bars) and low (white bars) levels of social support[42,43]

including chronic stressors, negative moods and social isolation, are associated with increased susceptibility to the common cold. They cannot be put down to any of a number of potential confounding factors that might vary alongside stress and thus account for differences in susceptibility. It is disappointing that direct evidence for immune mechanisms has yet to

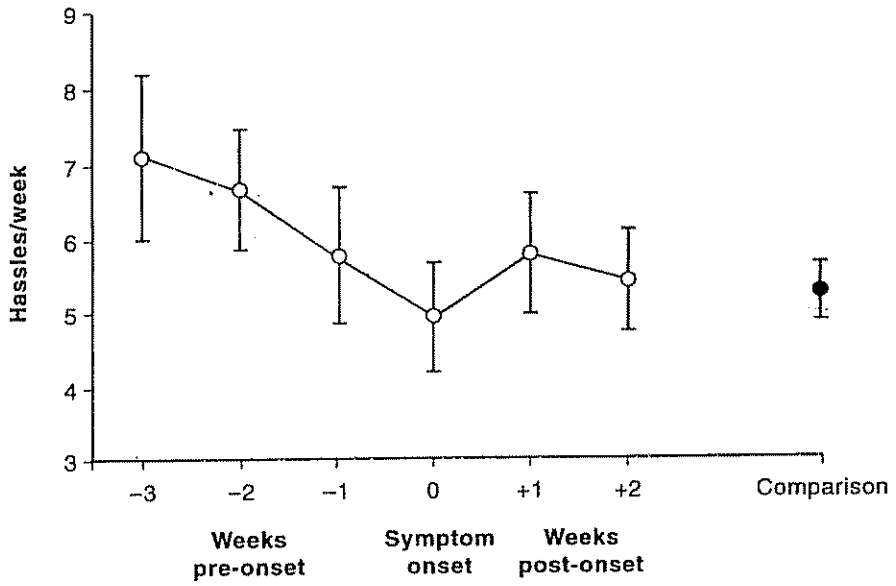

Figure 4

Associations between the number of hassles (minor stressors) reported per week and the onset of cold symptoms in children. Data points represent the mean number of hassles reported during the week of symptom onset (0), during one (–1), two (–2) and three (–3) weeks before symptoms, and during the first (+1) and second (+2) week after that in which cold symptoms appeared. The comparison value was averaged from children who did not contract a cold during the 15-week study period. Error bars are standard errors of the mean (SEM). (Reproduced with permission from Turner Cobb JM and Steptoe A[43])

emerge. Neuroendocrine variables and measures of immune function, such as T-cell counts, immunoglobulin levels and NK cell cytotoxicity, do not explain the findings. It may be that more subtle and specific types of immune response are involved, and Cohen and his colleagues are studying the possibility that stress influences the production of the pro-inflammatory cytokines, such as interleukin-6, thought to trigger symptom expression among infected subjects.

Naturalistic studies of stress and colds

Naturalistic studies of the relationship between stress and the occurrence of colds have been carried out in both adults and children[32]. For example, Graham *et al*[37] tracked 235 volunteers over six months and found that participants experiencing high levels of stress during the study had more episodes of acute respiratory tract infection than individuals with

low stress. In another study, Meyer and Haggerty[38] took regular throat cultures for streptococcal infection from members of 16 families and found that episodes of infection were likely to be preceded by disruptive family events. However, many studies of this subject suffer from the methodological problems outlined earlier, including an absence of measures of health behaviours, self-reporting of illness and retrospective designs[39–41]

Andrew Steptoe and Julie Turner Cobb attempted to take these factors into account in their evaluations of the impact of psychosocial factors on the occurrence of upper respiratory tract infection (URTI). Prospective longitudinal designs were used, so that psychosocial experience and URTI were assessed over several weeks. Episodes of URTI were verified through clinical examination, and negative affect was included as a control variable to reduce self-reporting biases. Health behaviours, such as smoking, alcohol consumption, exercise and sleep patterns, were repeatedly assessed throughout the study period so that their influences could be investigated.

One study lasted for 15 weeks and involved 107 adults and 116 children aged 5–16 years from 55 families[42,43]. Assessments of life events, minor stressors, social supports, coping styles and mood were made with different standardized measures for adults and children. Life events were assessed for the study period itself, while measures of social supports and the ways in which people typically coped with stress were obtained at both the start and finish of the investigation. Participants also completed weekly measures of minor stressors or hassles and daily URTI symptom checklists. Each family was visited at three-weekly intervals to monitor progress and to obtain measures of mood. In addition, visits were made whenever an URTI occurred in a family member and clinical examinations were carried out. When people had colds, detailed diaries of the number, duration and intensity of symptoms were maintained, together with records of changes in health behaviours and medication use.

During the study period, 27.1% of adults and 35.3% of children developed colds that could be clinically verified. A number of other episodes of symptoms were reported, but these could not be verified, usually because the individual was away from home and could not be examined. These latter episodes were excluded from the analysis as they might not have fulfilled objective criteria. Analyses of the results in both adults and children indicated that people who suffered from colds had more stressful experiences during the study period than the others under investigation. However, the impact of life event stress was moderated by perceptions of social support. The findings are illustrated in Figure 3, where an interesting parallel between adults and children is apparent despite differences in measures. Among individuals who experienced little life event stress during the study period, social support was protective and was associated with reduced susceptibility to colds. However, among participants experiencing high degrees of life stress, the levels of infection were similar in

those with good and poor social support. These associations were independent of control variables, such as age, gender, family composition and mood.

In this study, social support only appeared to be protective under conditions of low life event stress. The reason for this finding is unclear. It may be that life event stress and social support are not independent. Life events include serious marital disruption (for adults) and hospitalization of siblings (for children). In the face of such events, expectations of high social support may not be fulfilled as social networks are disrupted. People who believe they have good social support may not have access to this when it is needed. A second possibility is that people with supportive networks intensify their contact with friends and relatives when confronted with life stress, thereby increasing their exposure to respiratory tract infections; paradoxically, the acquisition of a cold may be more likely under such circumstances. In neither adults nor children were the associations between psychosocial factors and the occurrence of colds mediated by changes in health behaviours, such as smoking or exercise. Interestingly, however, the susceptibility to colds was greater among adults who did not drink alcohol than in moderate or occasional drinkers. A similar pattern has been observed in experimental studies of viral challenge[34,44].

The design of the study allowed both in-subject and between-subject effects to be evaluated. Figure 4 illustrates the changes in the number of hassles reported by children in the weeks before and after the onset of a cold. Hassles included being told to tidy their room or a friend at school being unkind. The number of hassles per week reported by participants who did not have a cold during the study period is illustrated for comparison. It can be seen that children reported a greater number of minor stressors than usual in the two to three weeks preceding symptom onset. This timing is consistent with the idea that immune defences need to be inhibited for several days before infection for a cold to develop.

Unfortunately it was not possible to assess immune responses in these naturalistic studies. The challenge now is to develop a comprehensive research design that includes standardized measures of life stress, social and psychological coping resources, immune function and objective measures of infection so that the complete sequence can be identified.

Stress and cold symptoms

The discussion so far has focused on the issue of whether or not psychosocial factors influence susceptibility to colds or the occurrence of illness. There is, however, a second important issue, namely whether or not psychological factors affect the subjective and objective symptoms of URTI. The number, severity or duration of symptom episodes may

relate to stress, personality or coping style, and knowledge of these links will help us to define further the extent of relationships between stress and colds. Both the experimental and naturalistic research strategies have thrown light on this topic.

Cohen *et al*[45] examined the impact of negative affect on symptoms in 53 volunteers who were administered rhinoviruses or influenza viruses. 'Negative affect' is the term used to describe undifferentiated subjective dysphoria and distress. As negative affect generates a 'plaintive set' or tendency to report somatic complaints and life stress, it is often regarded as a nuisance variable in psychosocial research[29]. Cohen *et al* used mucus weight collected on tissues as an objective measure of symptomatic status so they were able to compare influences on subjective and objective symptoms. They distinguished between trait negative affect (seen as a stable individual difference in psychological function) from state negative affect (a transient state of negative mood disturbance). It was found that trait negative affect was positively associated with the number of symptoms reported over the days following the administration of viruses. The relationship between trait negative affect and symptoms seemed to be relatively independent of objective symptoms, and may have been due to individual differences in cognitive processes, such as perception and appraisal. People who have a general tendency towards distress and low mood may be more likely to interpret bodily sensations as symptoms, and thus to report more extensive problems when they are ill. In contrast, state negative affect at the beginning of the study was found to predict not only subjective complaints but also mucus weight. It appears, therefore, that individuals experiencing greater levels of negative mood than usual at the start of the study developed more serious colds than those whose moods were positive, possibly because of poorer immune defences leading to more severe infection.

Turner Cobb and Steptoe[43] investigated another aspect of psychological function in relation to symptoms, namely coping disposition, in their study of naturally occurring colds. 'Psychological coping' refers to the cognitive and behavioural responses that people mobilize in an effort to manage potentially stressful events. It encompasses a range of responses, from the active planning of methods to deal with the situation through seeking social support to strategies such as distraction, wishful thinking and positive reinterpretation of events. Turner Cobb and Steptoe asked children about the ways in which they generally tried to cope with stress. They identified three broad dimensions:

- problem-focused coping, reflecting tendencies to cope by problem-solving and rethinking difficulties in a positive way
- emotion-focused coping, involving responses such as wishful thinking and blaming others
- avoidant coping, relating to the tendency to cope by distraction and social withdrawal.

These three dimensions are similar to those that have been recognized in studies of the way adults cope with stress[46] It was found that both problem-focused and avoidant coping were related to the duration of colds, but in different ways. Children who dealt with stress using problem-focused coping strategies tended to suffer from colds for a relatively short time. The sample was divided into high and low problem-focused copers by median split and adjusted statistically for gender, age, family composition, social class, parental smoking and alcohol consumption. It was found that colds lasted for an average of 6.97 days (standard deviation [SD] 3.9) in the high problem-focused coping group and 12.3 (SD 3.9) days in low problem-focused coping users. It is possible that individuals who tend to cope with stress by systematic efforts to solve the problem behave more appropriately in terms of self-care, for example by using nasal decongestants and reducing activity, thus limiting the duration of symptoms. In contrast, high levels of avoidant coping were associated with longer colds. After adjustment for other variables, the children who reported that they typically used avoidant coping strategies experienced symptoms for an average of 11.3 (SD 4.2) days, while the colds in non-avoidant individuals lasted for 7.01 (SD 4.4) days. This effect of avoidant coping was statistically independent of the problem-focused results. Perhaps people who use distraction and avoidant coping strategies fail to respond directly to their illness and do not take the necessary steps to prevent lengthy episodes of symptoms. An alternative explanation is that immune defences mounted after acquisition of the infectious illness are influenced by coping responses, and that this affects the duration of colds.

Conclusions

There is no doubt that the field of psychoneuroimmunology holds exciting prospects in terms of understanding how stress and other factors influence host defences and susceptibility to colds. There is growing evidence that psychosocial factors do influence susceptibility to colds, and that both potentially stressful events and the personal resources mobilized by individuals to come to terms with problems in life have an impact on vulnerability. Psychosocial factors are also related to the intensity and duration of cold symptoms, with mental traits and coping styles being particularly relevant. The impact of stress on colds is probably not due to variations in health-related behaviours, such as smoking, diet or sleep pattern. It is tempting to conclude that the effects on colds are mediated by immune processes. However, the precise immune pathways responsible are not yet known, and the next research priority is to identify the intervening steps. Once these mechanisms are understood we will be in a stronger position to develop ways of reducing susceptibility to the common cold by psychosocial means.

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