Common Respiratory Tract Infections as Psychological Entities: A Review of the Mood and Performance Effects of Being Ill

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The clinical manifestations associated with colds and influenza overshadow the equally important mood and performance impairments. While decreased alertness and increased anxiety can be considered side effects of symptomatology, symptoms alone may not be responsible for the psychomotor and attention deficits of colds and influenza, respectively. An alternative hypothesis, as proposed in this review, suggests that the immune response, in the form of a cytokine cascade, may be responsible for both the physical and psychological symptoms. In particular, patterns of cytokine production for each infection will dictate the symptoms and performance deficits both within and between viruses. This hypothesis can be extended to incorporate infectious mononucleosis, as well as colds and influenza. The efficacy of symptom-based over-the-counter medications is then called into question.

Upper respiratory tract infections (URTIs), such as influenza and the common cold, are the most frequently experienced infections in humans, with a typical adult suffering from two to five such infections per year (Sperber, 1994). A person suffering from one of these infections will typically report a general state of unwellness, which includes a decrease in normal levels of functioning, but the objective reality of associated psychological and behavioural impairment is not widely appreciated.

Colds and influenza are often considered to be synonymous by popular culture but the two are in fact clinically distinct entities (Kirkpatrick, 1996). The flu, for example, is caused by subsets of the influenza virus (e.g., the 1918–19 epidemic was caused by a strain of Influenza A). The common cold, on the other hand, is a conglomerate of symptoms caused by a number of different pathogens (predominantly rhinoviruses, but also coronavirus and respiratory syncytial virus, to name a few).

The familiar clinical manifestations of a cold are typically located at the site of the infection, with nasal discharge and stuffiness predominating. An influenza virus also exhibits such symptoms, albeit to a greater degree, but this infection is usually accompanied by a strong systemic response, including fever, malaise, headache, and possible myalgia. The psychological features of both influenza and the common cold may not be as consciously familiar. These generally take the form of depressed mood and reduced alertness, psychomotor impairment and a decrease in attention.

The aim of this review is twofold. As there have been no reviews on the psychological side-effects of an URTI since Smith (1995), and no critical review since Savory (1992), an initial aim here is to update the literature. Following this, an attempt is made to expand on the current theoretical position by putting forward a plausible hypothesis, encompassing the physical and psychological symptoms of an URTI. Specifically, it will be proposed that the immune response, in the form of cytokine production, may play a causal role in the production of each.

The Effects of Colds and Influenza on Mood

The literature demonstrates that the common cold and influenza both have a negative effect on mood ratings. Specifically, Smith et al. (1992) found that infection with an influenza B virus resulted in a general increase in negative affect (including anxiety and depression, together with a decrease in alertness and hedonic tone). In contrast, the common cold was shown to result in a reduction in subjective alertness, prompting Smith et al.'s conclusion that the nature of the viral infection (i.e., the clinical syndrome, such as "the common cold") dictated the mood changes.

One study that focussed exclusively on cold-producing pathogens compared a rhinovirus-infected group with coronavirus-infected participants, those with an unidentified cold, and healthy controls. Smith, Thomas, Kent, and Nicholson (1998) found that mood ratings from the three infected groups were not significantly different from each other, with each group feeling "significantly less alert and [having] lower hedonic tone than the healthy controls" (p. 736). A similar between-groups comparison in Smith et al.'s (1992) mood study, however, found "little evidence" (p. 208) of an increase in negative affect for two different rhinovirus serotypes but a significant decrease in alertness for the coronavirus group. Drake et al. (2000) also found no evidence of mood disturbance for rhinovirus type 23, using the Profile of Mood States (POMS) rather than the bipolar ratings used by Smith and colleagues.

The discrepancies in the literature regarding rhinovirus and coronavirus comparisons may be due to the clinical severity of each infection, a possibility that is also considered by Smith et al. (1998). There was no indication in either of the above studies that an analysis of symptom

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differences between the experimental groups had been undertaken, even though a coronavirus-induced cold is considered to be more physically severe than a rhinovirus (Kirkpatrick, 1996). It is unclear, then, whether the mood differences between virus types, and indeed the mood effects as a whole, are related to symptom severity or not.

The limited amount of research that has utilised symptom scores in the analysis shows moderate to highly significant correlations between mood and symptoms, suggesting that the negative mood effects increase as symptom severity increases (Smith et al., 1998, 1999). Smith et al. (1998) have suggested that these correlations may simply reflect individual differences, as each measurement is made through subjective ratings.

In support of the correlational data, there is little or no evidence that mood is affected during the asymptomatic phases of an illness when any symptoms present are too mild to justify classification of a clinical infection (Smith et al., 1992). During a subclinical illness, Smith et al. (1992) found no indication of mood effects in rhinovirus, coronavirus, or respiratory syncytial virus infections. There was also no evidence that the different cold-producing viruses influenced mood ratings during the incubation period. When clinical symptoms are minimal or nonexistent, then, mood ratings from an infected group do not differ from the controls.

Finally, it can be argued that a number of associated physical states other than the viral infection itself may influence a participant's mood. Sleep deprivation and sleep fragmentation, for example, have been found to have a significant effect on mood. In a meta-analytic review, Pilcher and Huffcutt (1996) found that partial deprivation, or sleep fragmentation, had "a considerably greater overall impact" (p. 322) on mood than long-term deprivation. Varied sleep patterns, in the form of increased slow-wave and decreased REM sleep, are also a common feature of illness (Hart, 1988, also see Mullington et al., 2000), these sleep phases being considered restorative for physical and cognitive functioning, respectively (Graves, Pack, & Abel, 2001; Roth & Roehrs, 2000). The overall quality of sleep may then be reduced during times of illness, as supported by Drake et al. (2000), who demonstrated significant decreases in total sleep time and sleep efficiency in volunteers challenged with a rhinovirus. Pilcher, Schoeling, and Prosansky (2000) also found significant correlations between sleep quality and subjective ratings of alertness, although the Drake et al. results did not support this. Hence, the possibility that the URTI-associated depressed mood is a result of disrupted sleep patterns and a subsequent decrease in sleep quality cannot be discounted.

In summary, the research by Smith and his colleagues suggests that mood is not an exclusive or independent psychological product of an infection. Rather, the decrease in mood states, such as alertness, may simply be a side effect of individual symptoms such as illness-associated variability in sleep patterns, or of symptomatology as a whole.

The Cognitive or Performance Impairments

The performance data from URTI research has encompassed impairment in tasks requiring fine motor control or the need for sustained attention. Smith, Tyrrell, Coyle, and Willman (1987) have clarified these findings further by suggesting that the type of impairment, either psychomotor or attentional in nature, may be virus-specific. Smith, Tyrrell, and Coyle, et al. proposed that the common cold predominantly causes impairment in psychomotor functioning, with performance on simple reaction time tasks being affected. On the other hand, influenza was argued as primarily affecting attention, with deficits occurring in tasks where the spatial or temporal location of the stimuli is unknown (Smith et al., 1998).

A number of memory tasks, including free recall, digit span and semantic processing, have also been utilised and two marginal effects were reported following rhinovirus challenge, regarding the recognition of thematic material (Smith et al., 1990). A general absence of memory effects for both colds and influenza, however, seems to have discouraged further investigation by that research group. Nevertheless, Capuron, Lamarque, Dantzer, and Goodall (1999) report memory deficits associated with a "flu-like syndrome" (p. 293), these being found primarily on tasks involving the immediate and delayed recall of a newspaper article, but also for picture recognition. As this finding coincides with that of Smith et al., further research into memory problems associated with an URTI may be warranted.

The generalisation about differences between the common cold and influenza arrived at by Smith and his colleagues, however, could be premature. A brief but critical review of their research, by Savory (1992), identified a number of methodological problems, all of which may limit the reliability of Smith's data. For example, despite the consistent use of analysis of covariance, individual variations may have been amplified by the small sizes of the infected groups, which therefore may not be representative of the general population (e.g., Smith, Tyrrell, & Coyle, et al., 1987, who had an influenza B group of three participants). Savory (1992) also considered the classification of uninfected participants as healthy controls to be problematic as they, too, had been inoculated with the virus. An apparent lack of matching of the controls to the experimental group may add to the classification problems, as parameters such as age and gender are considered to be influential on performance under certain conditions.

A further examination of this literature identifies the "separation of different functions" between colds and influenza proposed by Smith, Tyrrell, Coyle, Higgins, and Willman (1988, p. 415) as one that may not be entirely clear-cut once the tasks themselves are considered. Hall and Smith (1996a), for example, have classified their focussed-attention task as attention-based but the temporal and spatial location of the stimulus are known. The task simply requires the use of predominantly psychomotor functions in the form of responding appropriately (pressing either the A or B key on a keyboard) to the presentation of each stimulus. Consistent with this description is the finding that colds rather than influenza impaired performance on this task (Smith et al., 1989). Furthermore, Drake et al. (2000) found that rhinovirus-infected participants showed significant impairment in their performance on a vigilance task, a test of sustained attention, which contradicts the findings of Smith, Tyrrell, and Coyle, et al. (1987). Finally, both colds and influenza have been reported to impair performance on an attention-based categoric search task. It may be suggested, then, that attention deficits are not exclusive to influenza, and problems in psychomotor functioning are not limited to the common cold.

The above studies all consider functional differences between the common cold and influenza infections, but a variation has also been observed between two cold-producing pathogens. It was shown that a coronavirus and a rhinovirus both produced impairment on the same tasks but differed in the severity of that deficit. More specifically, a comparison of the two infection groups by Smith, Tyrrell, and Coyle et al. (1987) showed a greater level of psychomotor impairment by the rhinovirus pathogen. This finding has

not been replicated, though, as Smith et al. (1998) did not compare their coronavirus and rhinovirus groups on performance parameters.

The research discussed to this point has been limited to data where the infecting agent has been identified either through virological techniques with naturally occurring infections, or through a virus challenge. If studies are considered in which the infecting agent is not known, the results and hence the distinction become even less reliable, as subject groups may contain a number of cold and influenza viral strains. In particular, a sample that includes both cold and influenza sufferers (which it appears could be the case in the Hall & Smith, 1996a, study) may produce more generic deficits, rather than demonstrating virus-specific patterns of impairment, or may mask the effects altogether. A further problem with this type of research is that the definition of what constitutes an URTI is more open to individual interpretation (Hall, 1995), resulting in the misdiagnosis of allergic rhinitis and other health problems that can be confused with colds.

While an argument can be made for the existence of a trend, it cannot yet be concluded that impairment on attention-based or psychomotor-based tasks is exclusive to influenza and colds, respectively. Hence, Smith, Tyrrell, Coyle, Higgins, and Willman's (1988) claim of a "dissociation of psychological functions" (p. 415) by the different illnesses is not supported. In order for future work in this area to contribute to our knowledge, more stringent control is needed over the type of tasks used, as well as what constitutes a healthy participant. Notwithstanding these limitations to existing knowledge, however, performance impairment by URTIs seems well established, so what might be the cause?

Symptoms and the Performance Impairment

There is the contention throughout the work of Smith and his colleagues in the area of behavioural virology, that the mechanisms underlying performance impairment in colds and influenza must be different. This is based on the idea that performance can vary due to a change in state, such as circadian variation brought on by shift work, or the use of drugs (Hall & Smith, 1996a; Smith, Tyrrell, & Coyle et al., 1987). Influenza and the common cold are thought to produce different physical states and it was initially suggested that this alone might lead to the differential changes in performance.

Despite the plausibility of the argument that physical symptoms caused the performance impairment, the evidence suggested a possible dissociation between the two. Results from Smith, Tyrrell, and Coyle, et al. (1987) implied that differences in objective measures of symptom severity between a rhinovirus and a coronavirus infection were unrelated to severity of impairment. Smith et al. (1998) supported this result by showing that discrepancies in simple reaction time were not significantly correlated to reports of symptom severity or the amount of nasal secretion, but neither study provided a statistical comparison between the rhinovirus and coronavirus infections on a measure of symptom severity. A full picture of the relationship between symptoms and impairment in this context may in fact require both between- and within-virus comparisons. No definitive conclusions can therefore be made on the basis of the two studies, regarding severity of both symptoms and impairment.

Another approach to the question of a symptom and impairment relationship has utilised diurnal variations in symptomatology and performance measures. A virus-challenge study by Smith, Tyrrell, Coyle, Higgins, and Willman (1988) found that body temperature and the use of paper handkerchiefs was at its greatest during the morning, for influenza B, a rhinovirus and a coronavirus infection. In a later study of naturally-occurring infections, Smith, Thomas, and Whitney (2000) supported this by showing that the general severity of cold symptoms peaked during the morning. The latter study, however, also found reaction time to be at its slowest during the afternoon and therefore out of symmetry with the physical symptoms. The results suggest, then, that "factors which influence the severity of symptoms do not control the extent of the performance effects" (Smith, Tyrrell, Al-Nakib, et al., 1988, p. 70).

Research has also shown impairment to be present during the so-called "asymptomatic" phases of the incubation period and the subclinical infection. Smith, Tyrrell, Al-Nakib, et al. (1987), for example, found impairment during the incubation of a respiratory syncytial virus, coinciding with the type of deficits during the symptomatic phase. While Smith, Tyrrell, Al-Nakib, et al. (1988) did not replicate these findings in a subclinical version of the same cold-producing pathogen, influenza B was shown to impair performance during both a clinical and an asymptomatic infection.

The evidence of performance deficits in the absence of clinical symptoms is a compelling argument for dissociation between URTI-associated impairments and symptomatology. The definition of an infection as "clinical", however, as adopted by the Common Cold Unit, from Beare and Reed's (1977) method of classification, suggests that a small number of mild symptoms may still be apparent. Research of a more immunological nature has also utilised a similar method, with most referring to a clinical cold as an illness that has accumulated a specific number of points on a Symptom Scale. Zhu, Tang, Gwaltney, Wu, and Elias (1997), for example, classified participants as having a clinical cold if their Total Symptom Scores were ≥ 5 plus either nasal discharge for 3 days or the subjects' belief that a cold had occurred. As such, the distinction between a clinical and a subclinical infection is arbitrary and rather subjective.

Harris and Gwaltney (1996) also supported the possibility of symptoms during the asymptomatic phase of an infection. Their study on the incubation period of a rhinovirus infection found that some symptoms were present as early as two hours following inoculation. Shibayama et al. (1996) also found an increase in mucus production in the asymptomatic group. Furthermore, there is evidence to suggest that the severity of impairment varies between the symptomatic and asymptomatic phases. In particular, influenza B impairment was more severe during a clinical infection and less severe in the incubation period or a subclinical infection (Smith, Tyrrell, Al-Nakib, et al., 1988). Circumstantial evidence suggests, then, that symptoms are present during the so-called asymptomatic phase of an illness, and therefore may still be involved in impairment. The nature of the symptoms in both influenza and the common cold, though, may contraindicate any causal role this aspect has with impairment, as these infections are not always distinguishable on clinical grounds (Nicholson, 1998).

In the introduction to this review, a distinction was made between the clinical aspects of influenza and the common cold. Indeed, it was stated that colds were typified by nasal symptoms whereas influenza was characterised by both local and systemic features. Kirkpatrick (1996) stated, however, that colds produced by a coronavirus might also exhibit more systemic features, as well as the common nasal problems. If colds and influenza can each be associated with

both symptom groups, how can any distinction between the two with regard to impairment be explained? As such, the evidence for a causal relationship between symptoms and impairment is currently inconclusive and it may simply be that individual factors contribute to the impairment, rather than cause it.

A further possibility is that the immune response may cause both the symptoms and the impairment. Research supports this, as will be discussed in the following section. The question, then, is if each infection contains both types of symptoms, how can the different impairment profiles of the common cold and influenza be explained?

The Immune Response and Performance Impairments

It was initially proposed that the symptoms of an infection, such as influenza, were a result of the infecting agent itself, and the damage that the pathogen inflicted on the nasal epithelium. Research over the past decade, however, has lent credence to the theory that it is in fact the immune system's response to the invading pathogen that causes the familiar symptoms of such an infection (see Sperber, 1994).

An innate inflammatory cascade is induced upon infection, being activated when infected epithelial cells release a number of cytokines and other mediators (Hendley, 1998, Kuby, 1997). These cytokines act as messengers to promote the activation and migration of cells to the site of infection (Gabay & Kushner, 1999). The recruited cells then release more cytokines, which perpetuate the cascade. In particular, the interleukins (IL)-1 and 6, as well as tumor necrosis factor-α, are considered to be part of the first wave of the inflammatory response (Kuby, 1997).

Cytokines are also thought to play a major role in both symptom formation and sick behaviour. IL-6, as an example, is considered to be a strong inducer of the fever response, while anorexia, insomnia or increased somnolence, and loss of interest in grooming and socialising in animal studies have been association with a proliferation of mediators (see Vollmer-Conna, 2001, for a review). Research supports cytokines as a mechanism of symptomatology by showing a temporal relationship between cytokines and symptom groups (e.g., Yoon, Zhu, Gwaltney & Elias, 1999, observed a temporal relationship between IL-1 and symptomatology during a rhinovirus infection). The correlational nature of this data does not allow for any causal inferences, though, which has led to the use of a cytokine-challenge experimental model.

A cytokine-challenge, which involves introducing a specific cytokine into the nasal passage of a participant, demonstrates that the cytokine will, itself, produce a number of URTI-like symptoms. A study by Douglass et al. (1994), for example, found a significant general effect of nasal symptoms, based on a total symptom score, when challenging participants with IL-8. Proud et al. (1988) were able to define the symptom-cytokine relationship further by using bradykinin, another proinflammatory mediator. A spray of bradykinin into the nasal passages caused symptoms similar to that of a cold, as well as a sore throat.

Smith, Tyrrell, Coyle, and Higgins (1988, 1991) have used the cytokine-challenge technique to investigate the effects of the interferon (IFN)-α on performance. Interferons are antiviral cytokines that infected cells release in order to warn and protect nearby healthy cells. When IFN-α is used as an antiviral treatment, influenza-like side effects on health have been observed, such as fatigue. Smith et al. speculated that IFN-α, as a cytokine involved in a systemic immune response, might be able to account for the influenza impairment through interaction with the CNS and, more specifically, the frontal lobes.

The results of the two IFN-α studies found deleterious effects on physical wellbeing, mood, and performance. Physically, the highest dose of interferon (1.5 MU) produced a significant increase in both pulse rate and sublingual temperature (Smith, Tyrrell, Coyle & Higgins, 1988, 1991). This concurs with the finding that a number of cytokines, including IFN-α, are "intrinsically pyrogenic" (Dinarello, 1997, p. 90). Subjective ratings of alertness were also significantly decreased by three separate doses of the cytokine, suggesting that the interferon is producing effects similar to influenza (Smith, Tyrrell, Coyle & Higgins, 1991).

The performance data is less easy to interpret in this manner. In line with the research on influenza, performance on the variable foreperiod simple RT task was impaired by the highest dose of IFN-α (Smith, Tyrrell, Coyle & Higgins, 1991). The highest dose experimental group also performed significantly more slowly on a pegboard task, although only on the day following cytokine-challenge. However, this task had previously been utilised to measure hand-eye coordination, with performance only impaired by colds (see Smith, Tyrrell, Al-Nakib, et al., 1988). Further, performance on a search task that had previously been impaired by influenza was not affected.

Both studies clearly demonstrate a detrimental effect of cytokine-challenge on performance. Due to the reported impairments associated with IFN-α, though, it was acknowledged that this cytokine alone could not account for the differential impact of colds and influenza on cognitive and psychomotor functioning (Smith, Tyrrell, Coyle & Higgins, 1991). This conclusion is supported by Färkkilä et al. (1984, cited in Smith, Tyrrell, Coyle & Higgins, 1991), who found that the chronic effects of IFN-α encompassed problems with learning and memory, the slowing of reaction time, and the coordination of hand-eye movements. Poutiainen, Hokkanen, Niemi, and Färkkilä (1994) also showed deteriorated memory and concentration skills following challenge with IFN-α. In contrast, Capuron, Ravaud, and Dantzer (2001) found no detrimental effects of IFN-α, administered intravenously, on tasks of spatial working memory or planning and problem solving but did show significantly retarded reaction times on a task equivalent to Smith, Tyrrell, Al-Nakib, et al.'s (1987) serial response task.

The obvious functional differences between Smith, Tyrrell, Coyle, and Higgins (1991) and the other studies, as well as that between the cytokine-challenge research and the reality of colds and influenza, may simply be due to the levels of interferon present. While it may be argued that the skills being impaired all require a degree of attentional resources, greater levels of interferon may have greater impact, thus producing impairment at higher levels of cognitive functioning.

A further problem with the cytokine-challenge studies as a whole, is that it may be possible that the introduced cytokine — whether it be IFN-α or another mediator — might activate the cascade prior to symptom formation. As part of the inflammatory cascade, cytokines do not function independently but rather work in conjunction with and often synergistically with each other (Gabay & Kushner, 1999). Furthermore, many cytokines are able to initiate and control the production of others (e.g., IL-1 and tumor necrosis factor-α are able to induce the production of IL-8), indicating that these mediators may function as a network in order to generate the immune response. This implies that IFN-α alone, for example, would not cause an entire profile of impairment, but rather would act with other cytokines in order to do so, which is supported by Smith, Tyrrell,

Coyle, and Higgins's (1991) study. Hence, the cytokine-challenge methodology in this context might only demonstrate that the cytokine cascade as a whole is responsible for the performance decrements, rather than any specific cytokine.

A comparison of different infection types also suggests that an increase in the production of specific cytokines may be a general phenomenon in viral upper respiratory infections. Noah et al. (1995) investigated the presence of the interleukins 1β, 6, and 8, as well as tumor necrosis factor-α, in children with naturally occurring infections. By using two experimental groups (those who were infected with a respiratory syncytial virus and those who were infected with another cold-producing virus), the study was able to demonstrate that all four cytokines were present, regardless of the viral strain present in the volunteers. A comparison of the literature on rhinoviruses and influenza A also indicates that a number of cytokines may be part of a generic response to any URTI. This same comparison, however, has led to the conclusion that the timing and intensity of production of each cytokine appears to differ between different viruses. This discrepancy, in turn, may coincide with the differing profiles of performance impairment between rhinovirus infections and influenza.

The generation of IL-8 was observed to vary between influenza and rhinovirus infections in the degree at which levels increased and peaked. Turner, Weingand, Yeh, and Leedy (1998) and Zhu et al. (1997) both found a peak in IL-8 production by Study Day 2, or 48 hours after inoculation with a rhinovirus pathogen. In contrast, infection with an Influenza A virus led to a more sustained increase of IL-8, with a delayed peak manifesting at Day 4 or 5 (Hayden et al., 1998; Skoner, Gentile, Patel & Doyle, 1999). Shibayama et al. (1996) also found an almost identical pattern in the production of bradykinin across the two infection types to the pattern of interleukin-8.

Any discrepancy in the production of IL-1 between colds and influenza, on the other hand, is less clear. This cytokine has been observed during a rhinovirus infection, with an increase in both IL-1α and -1β detected early on in the duration of the illness (Yoon et al., 1999). Furthermore, a naturally occurring antagonist of IL-1 (IL-1ra) was found to correspond with the resolution of the physical symptoms, prompting the suggestion that the host response may use cytokine antagonists, like IL-1ra, to clear both the viral agent and the induced immune response itself. The lack of a substantive rise in IL-1 during an influenza A infection, though, has led Hayden et al. (1998) to suggest that this cytokine may simply be "less important to symptom formation" (p. 647) during the flu.

The discrepancy in IL-1 production may be explainable through the function of each cytokine during particular viral infections. Research by Terajima et al. (1997) and Yamaya et al. (1999), for example, investigated a rhinovirus and its receptor (intercellular adhesion molecule-1, or ICAM-1) and found that certain cytokines act to increase the ICAM-1 levels at the infection site. IL-1 may simply be more relevant to the rhinovirus infection than influenza, as the latter infection does not utilise this receptor. Thus, discrepancies in cytokine production between infection types may be able to explain the psychological differences between colds and influenza. In fact, the possibility that virus-specific profiles of psychological impairment could be a reflection of virus-specific patterns in the immune response is something that demands systematic research.

The differences in cytokine production also extend not only to rhinovirus and influenza comparisons, but also to different rhinovirus serotypes. Sanders, Siekierski, Porter, Richards, and Proud (1998), in an in vitro study, compared four separate rhinovirus infections (type 14, 16, 39, 1A) on the measures of IL-6 and IL-8 production. Initial results showed an increase in the presence of the two cytokines for all four strains, but a closer inspection indicated type 16 induced, "a more rapid and robust production" (p. 936) of both IL-6 and IL-8, than occurred for the type 14 infection. In accordance with this finding, Tyrrell, Cohen, and Schlarb (1993) demonstrated some physical, or clinical, but non-significant discrepancies between several other rhinovirus serotypes, although similar comparisons have not been made in the performance literature. The data is thus conducive to the suggestion of patterns within the immune response to viral infections.

Finally, it is worth considering just how a specific pattern of cytokines might result in a specific pattern of symptoms and impairment. As mentioned earlier, cytokines are thought to function as a part of a cascade, combined with other mediators, rather than as independent factors. It appears likely — although this is conjecture rather than hard fact — that "informational content resides in the combinations, and perhaps sequence, of cytokines" (Mackiewicz, Speroff, Ganapathi & Kushner, 1991, p. 3032). That is, the patterns within the immune response may act as a form of sign language, with each pattern containing specific information. As a consequence, this informational content may dictate the clinical and psychological features of a particular infection, and thus dictate the differences between infections.

One of the overriding implications from the immunological literature is that the immune response to viral infections, in the form of a cytokine cascade, is the inducer of the well known physical symptoms. A further suggestion is that these cytokines are also responsible for decrements in performance. In view of the possibility that different patterns of cytokine production correspond to clinical and psychological differences between the common cold and influenza, would it not also be true that other viral infections, such as infectious mononucleosis, would exhibit the same trend?

Infectious Mononucleosis

There are only three published studies that investigate a range of performance impairments associated with infectious mononucleosis (IM) (Corney, Hale & Ball, 1994; Crocker, Ball & Montgomery, 1997; Hall & Smith, 1996b), with some similar and some contrasting results presented by each study. By investigating acute IM (defined as < 2 months since the onset of the illness), Corney et al. and Hall and Smith both found that performance on a variable foreperiod simple RT task was impaired. A significant effect for accuracy on a repeated numbers vigilance task was also reported by both studies, although they differed on the actual measure affected (hits or false alarms respectively).

From the results, Hall and Smith (1996b) suggested that impairments associated with acute IM were in fact similar to that of influenza. Crocker et al. (1997) found, however, that acute IM sufferers also exhibited impaired recall of semantic material, which is not the case with influenza sufferers. This finding is not supported by the earlier studies, though. Influenza and acute IM also differ quite markedly with regard to symptomatology. Acute IM features a "characteristic triad" of fever, pharyngeal inflammation, and inflammation of the lymph nodes at the neck (Hornef, Wagner, Kruse & Kirchner, 1995, p. 209), suggesting this to be a more physically severe viral infection.

Hall and Smith (1996b) also made a comparison between acute and chronic IM (defined as > 6 months since

the onset of the illness) and found that the two infected groups did not differ on a measure of symptomatology. It was suggested, however, that the majority of chronic IM sufferers might have felt as though they had not yet recovered from the acute illness, as they did not exhibit any characteristic after-effects. Differences were noted between the two on performance measures, though, suggesting a strong argument for dissociation between symptoms and impairment. Crocker et al. (1997) did not appear to find any significant differences between acute and chronic IM on a measure of symptom severity, or on tests of performance. Corney et al. (1994) attempted no comparison between the two IM groups, though, so this result cannot be validated at this time. A study by White, Dash, and Thomas (1998), however, found that the impairment on a measure of information processing decreased over a 6-month period, from the onset of IM, as did a subjective rating of concentration.

Due to the symptom differences between acute IM and influenza, and assuming that cytokines are responsible for symptomatology, differences in cytokine production would also be expected. No direct comparisons have been made between these infections but a consideration of the literature suggests that IL-1β, IL-6 and the interferons have been detected in acute IM (e.g., Schuster, Herold, Wachter & Reibnegger, 1993, found evidence for an initial burst of IL-6), as well as in colds and influenza. The number of discrepancies in the IM research (see Andersson & Andersson, 1993; Biglino et al., 1996) does not allow for a definitive conclusion but a possible generic response involving these cytokines may be tentatively proposed.

As expected, the pattern of cytokine production also shows some differences from influenza and the common cold. For example, tumor necrosis factor-α is thought to play a major role in IM-associated symptom formation (Hornef et al., 1995; Wright-Browne et al., 1998). IL-2 (Hornef et al., 1995) and IL-10 (Taga, H., Taga, K., Wang, Chretian & Tosato, 1995) have also been found during an Epstein Barr Virus-induced IM illness; two cytokines that have not been detected in influenza or rhinoviruses (e.g., Hayden et al., 1998, found little evidence of IL-2 production in influenza).

Furthermore, cytokine-challenge studies have been conducted using IL-2 within the framework of immunotherapy for cancer patients. Caraceni et al. (1992) and Lacosta, Merali, and Anisman (1999), for example, found evidence for impaired working memory due to an IL-2 challenge, although the latter was using a murine model. Capuron et al. (2001) extended these findings by showing that treatment with IL-2 produced deficits in spatial working memory and planning abilities. Reaction time remained unimpaired in this study, in contrast to Walker et al. (1996), who also demonstrated impaired vigilance. The latter finding, in particular, coincides with the cognitive deficits associated with IM, but it must be asked whether the levels of IL-2 used in these studies are substantially larger than those found in IM, which could explain the more severe memory deficits.

Research into the performance effects of infectious mononucleosis is still in its infancy. A number of inconsistent results in this literature and in that on cytokine production do not allow for any definitive conclusions, but instead point towards a trend. That is, a profile of symptomatology, performance impairments and cytokine production associated with infectious mononucleosis appears to differ from that associated with influenza and the common cold. This trend consequently supports the possibility that the immune system itself is responsible for symptoms and impairment of a viral infection.

Implications for Treatment of the URTI

Becoming ill from an URTI can result in work and school absenteeism, which alone has enormous economic bearings. An informal survey from a Tasmanian college currently employing 146 staff, as an example, showed that the equivalent of 74.5 working days were lost and another 179 were affected over a 2-week period due to a virulent but unidentified strain of URTI. The two main approaches in removing this, as with most health problems, are prevention and treatment. For influenza, vaccinations are now readily available and antiviral agents, which inhibit viral replication, are also considered to be effective. Such preventative measures are difficult to produce for the common cold, though, due to the vast array of cold-producing pathogens (the rhinovirus alone has 100+ serotypes) (Sperber, 1994). Furthermore, antiviral agents are most effective when taken immediately after exposure to the virus, rather than as a treatment once the symptoms are apparent (see Turner et al., 1999). Unfortunately, the onset of symptoms is usually the first sign that we are "coming down with something", so other treatments may still be necessary.

In both influenza and colds, over-the-counter medications are used in abundance as treatment measures and it is clear that consumers believe in the effectiveness of these medications (Smith & Feldman, 1993). While the alleviation of symptoms may be a priority, the literature highlighted in this review suggests that the psychological features of an infection cannot be ignored. Smith and members of the Common Cold Unit in the UK have studied both zinc gluconate lozenges and nedocromil sodium (Smith, Tyrrell, Al-Nakib, et al., 1991), the mechanisms of which are unclear, but there are no known studies on the impact of symptom-based medication on URTI-associated impairment. A brief consideration of the mechanisms underlying these treatments may provide an argument for or against their efficacy in this regard.

The mechanism of action for most traditional over-the-counter medications is a direct impact on symptomatology. Decongestants, such as pseudoephedrine, are sympathomimetic in nature and are considered to be effective by constricting blood vessels in the nasal passage and sinuses (Jawad & Eccles, 1998). This, in turn, leads to a reduction in nasal symptoms such as congestion (Taverner, Danz & Economos, 1999) and sneezing (Bye et al., 1980).

The antihistamines are also used in order to combat sneezing and rhinorrhea associated with URTIs, but while this group of compounds may be effective in treating seasonal allergies, many are considered to be little better than a placebo in treating the symptoms of a cold (Smith & Feldman, 1993). This general ineffectiveness is believed to be due to the absence of histamine in the immune response to viral infections. A review by Smith and Feldman highlighted several studies where a number of antihistamines (e.g., chlorpheniramine) reduced symptom scores but it is likely that such effects were due to the drying out of nasal secretions (Sperber, 1994) rather than an inhibition of the immune response.

Decongestants and antihistamines, as representatives of over-the-counter medications, are considered to alleviate physical effects of the URTI through a direct impact on symptomatology. As neither drug influences the immune system, traditional over-the-counter medications may have little benefit on the psychomotor and attention deficits, given the argument put forward by this review.

An easily accessible alternative treatment, which may prove beneficial for both the physical and psychological features of an URTI, is echinacea. Echinacea is an increasingly

popular herbal remedy with immunomodulatory properties (Melchart et al., 1995); that is, regulation or stimulation of the immune response. More specifically, this treatment is thought to "activate the immune system via cytokine pathways" (Burger, Torres, Warren, Caldwell & Hughes, 1997, p. 377), possibly by increasing the migration of cells to the site of infection. While this may lead to an increase in cytokine production, the level of cells present allows for greater elimination of the pathogen from the body before the infection can become fully established. Consistent with this proposal is the reduction in duration and severity of the illness as found by Barrett, Vohmann, and Calabrese (1999). Due to the properties underlying the efficacy of echinacea, the hypothesis can be made that this form of therapy could also alleviate the impairments associated with an URTI.

Conclusion

Common upper respiratory infections like colds and influenza can be characterised by a number of both physical and psychological features. The former symptoms are, of course, the discomfort of a runny and congested nose, and we generally feel lousy into the bargain, with a decrease in alertness and sociability. The studies by Smith and his colleagues have also highlighted a number of psychomotor and attention deficits attributable to colds and flu, respectively. While claims of a complete "dissociation of function" cannot be supported by the current literature due to methodological shortcomings, a pattern of impairment does appear to exist for each infection.

A consideration of the immune system's response to an infection, in the form of cytokine production, may be able to explain this pattern of impairment. Cytokines are thought to be involved in the formation of symptoms and Smith's work on IFN-α also suggests a causal role in performance deficits. It may be the differences in cytokine production between the types of viruses that lead to the observable patterns in both physical and psychological symptoms. More specifically, by involving a number of cytokines in conjunction with each other, the cytokine cascade acts as an informational network. The patterns within the response may determine both the clinical and the psychological features of a particular infection, and subsequently dictate the differences between infections.

If the immune system is, indeed, responsible for impairments in performance, the efficacy of standard over-the-counter treatments becomes questionable. Decongestants and other non-prescription cold medications are almost exclusively directed at symptomatology and the immune system is not interfered with. As a result, the major symptoms of a cold or flu may be alleviated while leaving the impairment intact. The issue of performance decrements then becomes important for medical and occupational reasons, as the symptoms are the major cause of absenteeism. Superficially effective common cold remedies may allow people to return to normal activities only to increase the risk of traffic or work place accidents.

The area of behavioural virology has begun to move away from defining the actual impairments and is now directed more toward the underlying mechanisms. A way to begin investigating the immune response as this possible mechanism may be through treatment paradigms. By using a number of symptomatic treatments and immunomodulators, the involvement of symptoms and cytokine production in URTI-associated performance impairments may be elucidated.

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