Review of the Literature: Integrating Psychoneuroimmunology into Pediatric Chronic Illness Interventions

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Objective Provide an orientation to psychoneuroimmunology, a rationale for including assessments of immune function in intervention studies of pediatric chronic illness, review the current literature, and provide recommendations for future research. **Methods** Using electronic searches and previous reviews, selected and reviewed published studies in which immunological changes related to psychological interventions were assessed in pediatric samples. **Results** Eight studies were identified and included in the review. These utilized a range of interventions (e.g., disclosure and hypnosis) and included a variety of pediatric samples (e.g., those with asthma, HIV infection, or lupus). **Conclusions** Results suggest that psychological intervention can influence immune function in pediatric samples. Recommendations for advancing our knowledge by studying populations for whom the immune system plays an active role in disease pathophysiology, measuring disease-relevant immune mediators, studying pediatric patients under times of stress, and focusing on interventions aimed at altering the stress system are provided.

Key words intervention; pediatric chronic illness; psychoneuroimmunology; review.

The field of psychoneuroimmunology (PNI) has grown dramatically over the past three decades as researchers and the lay public have become increasingly interested in the bi-directional associations between psychological and biological processes, as well as in the intriguing hypothesis that psychological factors influence disease initiation and course (Lovallo, 2005; Rabin, 1999). Researchers have sought to determine associations between psychological factors (e.g., stress, depression, hostility, and optimism) and diseases (e.g., hypertension, cancer, asthma, and the common cold), as well as between psychological factors and specific biological processes (e.g., biological stress response and immune function) that underlie medical conditions and might mediate the association between psychological factors and disease (see reviews by Herbert & Cohen, 1993a,b; O'Leary, 1990; Segerstrom & Miller, 2004). Most recently, psychological states, biological processes, and medical outcomes have been studied simultaneously in the same subjects (Broadbent, Petrie, Alley, & Booth, 2003). Concurrently, research has begun to address whether psychological intervention might alter biological systems and the course of medical conditions (see review by Miller & Cohen, 2001).

Unfortunately, the vast majority of PNI research has been with adult samples. In addition, many studies have not included subjects with medical conditions. Because children and adolescents experience the same psychological factors that have been the focus of PNI research, have biological responses to psychological factors, and are diagnosed with a variety of diseases for which the immune system plays a major role, the field is ripe for research by pediatric psychologists. The purpose of the current review is to (a) provide an orientation to the immune system and PNI research using findings from adult studies and a small number of studies of pediatric samples; (b) review studies that have evaluated the influence of psychological interventions on the immune system in pediatric samples; and (c) provide recommendations to encourage pediatric psychologists to integrate PNI methods into research examining the influence of psychological interventions on pediatric disease.

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Introduction to the Immune System and PNI Immune Analyses

It is first necessary to define and elaborate some of the key concepts, constructs, variables, and measurements that will be discussed throughout the article. For the purposes of this review, we will focus specifically on the associations between psychological factors and the immune system. A complete discussion of the human immune system and immunological methods, however, is beyond the scope of this article. The interested reader is referred to texts by Coico, Sunshine, and Benjamini (2003), Kuby (1997), and Sompayrac (2003) for more detail.

The task of the immune system is to protect the individual from invading organisms (e.g., bacteria and viruses) as well as from altered self-cells (e.g., cancer cells). Immune responses are enacted by a variety of cells, the most widely studied in PNI research being lymphocytes. Lymphocytes are a subset of white blood cells (WBCs) that are produced in the bone marrow, stored in various lymphoid organs (e.g., the spleen), and circulated in the bloodstream (Kuby, 1997). The three major lymphocyte types studied in PNI research are B cells (that produce antibodies), T cells (that support B-cell function and help eliminate altered self cells), and natural killer (NK) cells (nonspecific cells that, for example, play a role in defense against tumor cells). Lymphocytes (as well as other WBCs) also produce and release low molecular weight proteins, termed cytokines (e.g., the interleukins and interferons), which regulate the immune response through their effects on lymphocytes and other immune cells.

Given the numerous cells and products they produce, there are a variety of ways that changes in the immune system have been measured in PNI research. Although some immune products [e.g., secretory immunoglobulin A (sIgA)] can be measured in saliva, most immune analyses are conducted on peripheral blood collected from the subject. Prior to specific immune analyses, blood samples must be processed to separate WBCs from red blood cells and plasma. Once this is complete, two strategies are available to analyze the WBCs. *Enumerative* approaches quantify the amount of a particular immune parameter, for example the relative proportion of different cell types within the total WBC population, or the amount of a certain cell product contained in the cell or produced by it. Two major enumerative techniques are available. One is flow cytometry, during which a fluorescent antibody to the immune product of interest is added to the cell culture. Cells that have the immune product of interest will be ''stained'' with the fluorescent antibody. Using a fluorescence-activated cell sorter (FACS), subpopulations of lymphocytes can then be counted. The other major enumerative technique is enzyme-linked immunosorbent assay (ELISA), during which an enzyme attached to an antibody of the immune product of interest is added to the culture of cell products. The enzyme–antibody complex will bind to the immune product of interest. In this way, the concentration of the immune product can be quantified. Thus, *enumerative* approaches provide information about the numbers (or relative percentages) and types of cells present and the amount of specific immune products being produced by such cells.

Functional approaches (which can be used either instead of or in combination with enumerative techniques) determine the effectiveness of immune cells to proliferate and/or neutralize infected cells or altered self-cells. Two major techniques are available. One is lymphocyte proliferative response, during which lymphocytes are cultured with a powerful, nonspecific antigen (termed a mitogen) in a medium to which a radioactive substrate has been added. The mitogen serves to stimulate lymphocyte proliferation. As the lymphocytes proliferate they absorb the radioactive substrate, which can then be measured. This technique provides information about how well the immune system could proliferate lymphocytes to mount an immune response. The other major functional technique measures cell cytotoxicity, and provides information about how well cells of the immune system (e.g., NK cells) can destroy infected cells or altered self-cells, both of which would be deemed ''foreign'' by the immune system. In this technique, immune cells are cultured with target cells (e.g., infected cells) that have been labeled with a radioactive substrate. As the target cells are destroyed, their contents spill into surrounding supernatant. Results as to the number of immune cells needed to destroy a number of target cells are obtained.

PNI Studies in Adults

Although the effects of a variety of psychological factors on immunity, including depression (Herbert & Cohen, 1993b; Weisse, 1992; Zorilla et al., 2001), social support (Uchino, Cacioppo, & Kiecolt-Glaser, 1996), and personality (Segerstrom, 2000), have been studied, the effects of stress on immunity have been most widely studied. The focus on stress, typically operationalized either as a brief laboratory stressor (e.g., performing mental

arithmetic); an acute, but naturalistic stressor (e.g., academic exams); or as a chronic naturalistic stressor (e.g., caring for an ill spouse), likely results because psychological factors are theorized to have their effect on the immune system through their influence on the stress system. Stress has predictable effects on the autonomic and central nervous systems, activating the sympathetic–adrenal–medullary (SAM) system and hypothalamus–pituitary–adrenal (HPA) axis, resulting in the release of catecholamines (e.g., epinephrine and norepinephrine) and cortisol. Because WBCs, including lymphocytes, have receptors for catecholamines and cortisol, stress-induced release of these neuroendocrine products has the potential to influence immune function (Black, 1994; Rabin, 1999). For example, among a variety of effects, catecholamines suppress lymphocyte proliferation to mitogen, and glucocorticoids suppress antibody production, cytokine production, and NK cell activity.

Results from correlational PNI studies with adults demonstrate the complexity of conducting PNI research and highlight why empirical work with pediatric samples is also warranted (for comprehensive reviews, see Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Segerstrom & Miller, 2004). Even brief laboratory stressors (e.g., mental arithmetic or speech task lasting 10–30 min) influence immune parameters in blood collected immediately after the stressor, for example, increasing some circulating cell numbers. Although these changes may be transient, they nonetheless highlight how sensitive the immune system may be to perturbation, and how quickly it may begin mobilizing to address a threat. Acute, naturalistic stressors (e.g., an exam) have been shown to affect the immune response to immunization as well as the rate at which experimental wounds heal. For example, Marucha, Kiecolt-Glaser, and Favagehi (1998) showed that wounds placed on the hard palate of college students a few days before a major exam healed more slowly than wounds in the same individuals placed over summer vacation. More chronic naturalistic stressors produce similar immune changes, and have been shown to increase susceptibility to developing a cold when subjects are experimentally exposed to cold viruses. For example, results from Cohen, Frank, Doyle, Rabin, and Gwaltney (1998) suggest that work problems and chronic interpersonal difficulties with family or friends increase the likelihood of developing a cold after exposure to a cold virus. Subsequent data suggest that positive emotional state lowers the risk of developing clinical cold symptoms (Cohen, Doyle, Turner, Alper, & Skoner, 2003).

Other studies have assessed the role of psychological factors in chronic medical conditions such as autoimmune diseases, HIV, and cancer. Inconsistency of results among these studies may result from heterogeneity of research populations and medical conditions, subject factors such as age of participants, and whether disease initiation or course was the focus of study. For example, in a meta-analytic review, Duijts, Zeegers, and Borne (2003) conclude that an association between stressful life events and breast cancer risk is not evident. However, longitudinal studies of men with HIV (Leserman et al., 1999; Page-Shafer, Delorenze, Satariano, & Winkelstein, 1996) suggest that stress and depressive symptoms are prospectively associated with faster disease progression. Interestingly, in the sample studied by Page-Shafer et al. (1996), baseline depressive symptoms did not predict HIV disease progression 5 years postdiagnosis (although depressive symptoms did predict a decline in CD4 lymphocytes at that time), but did 9 years postdiagnosis. This underscores the importance of studying the effects of stress (and psychological interventions) on chronic medical conditions over longer periods of time than is necessary in studies of more acute conditions (e.g., colds), and also that immune changes may have cumulative effects that lead to disease symptoms at later points in time.

Additional research has sought to determine specific immunological changes that may explain how stress influences health outcomes, and it is now widely accepted that stress can influence immune function (see reviews by Herbert & Cohen, 1993a; Kiecolt-Glaser et al., 2002; Segerstrom & Miller, 2004; Zorilla et al., 2001). It is important to note that stressors of different types and of different durations produce different effects on the immune system (Herbert & Cohen, 1993a). Segerstrom and Miller (2004) suggest that stress may act to dysregulate the immune system rather than lead to overall immune enhancement or suppression. This idea has particular importance when one considers that many chronic medical conditions, including those experienced by children and adolescents (e.g., asthma and inflammatory bowel disease), are characterized by immune dysregulation (Neurath, Finotto, & Glimcher, 2002).

Some PNI research with adults has sought to identify psychological–immune-disease associations in samples of ill subjects, and also among older individuals because of the immune changes that are inherent in these populations. The major effort of these studies has been to determine whether psychologically-induced immune changes are sufficient to produce important changes in

health status. This sophisticated PNI research is in its infancy, but results are promising. For example, in studies of wound healing (Broadbent et al., 2003; Glaser et al., 1999) individuals under stress (whose wounds healed more slowly) also demonstrated lower levels of proinflammatory cytokines that are associated with wound healing. In addition, although not all results have supported an association between psychological factors and disease progression, among HIV+ men, those with chronic and severe depression showed greater declines in T-helper cells, a primary clinical indicator of disease progression (Kemeny, 1994). Finally, recent studies in aging populations suggest that interleukin-6 (a proinflammatory cytokine which is elevated in the elderly), plays a role in a variety of aging-related conditions, including cardiovascular disease (Volpato et al., 2001).

Do Psychological Interventions Influence Immune Function in Adults?

Miller and Cohen (2001) conducted a meta-analysis of 59 studies of the influence of psychological interventions on immunity. Only two studies of children (of five identified) met methodological criteria for inclusion. Thus, the review was almost exclusively focused on adults. Samples included people with chronic medical diseases, upper respiratory tract infections, upcoming exams, high scores on measures of hypnotic susceptibility, and/or past success with hypnosis. The psychological interventions evaluated were stress management (16% of studies), relaxation (26%), disclosure (10%), hypnosis with immune suggestion (31%), hypnosis with immune suggestion versus a relaxation intervention (7%), and conditioning (10%).

Miller and Cohen (2001) found modest evidence that psychological interventions influence immunity. Studies revealed a change in some features of the immune response, but not others. The only immune change to occur across two different psychological interventions (i.e., relaxation and hypnosis with immune suggestion) was an alteration in sIgA in saliva. Because sIgA is the major antibody in secretions, acting as the first line of defense against pathogens at mucosal surfaces (e.g., the respiratory and gastrointestinal tracts; Coico et al., 2003; Cunningham-Rundles, 2001), decrements or enhancements of sIgA could influence susceptibility to and/or course of infection (Hewson-Bower & Drummond, 2001). The most consistent evidence of immune alterations was with hypnosis with immune suggestion and conditioning trials. There was mixed evidence of immune alteration with stress management and disclosure, and little immune change with relaxation. Conceptual and methodological improvements to the literature including better matching of subjects to interventions (e.g., using stress management interventions with those experiencing severe or chronic stress) and better evaluation of treatment integrity (e.g., are those subjects in a relaxation intervention actually exhibiting evidence of a relaxation response?) were recommended.

Rationale for PNI Research in Pediatric Samples

Although pediatric psychologists are highly interested in stress (La Greca, Siegel, Wallander, & Walker, 1992), psychological interventions (Drotar, 2006), and health outcomes (Roberts, 2003), very little research has evaluated the influence of psychological factors and interventions on immune function in pediatric populations. Several reasons may explain this lack of research. First, pediatric psychologists may not collaborate with basic scientists (e.g., immunologists) needed to help design and conduct such studies. Second, pediatric psychologists may feel ethically opposed to subjecting children with chronic diseases to unnecessary stress, either in the form of laboratory protocols or medical tests. Third, the cost of adding additional immune analyses is significant and may not be perceived as being central enough to hypotheses to warrant the additional cost. Fourth, pediatric samples may be difficult to recruit, perhaps because venipuncture is often necessary to collect samples for immune analyses.

Despite these possible barriers or concerns, the rationale for studying the effects of psychological factors and interventions on the immune system in pediatric samples derives from several areas. First, as noted above, the mechanism of action proposed for the benefit of psychological interventions on the immune system is through alteration of the stress system. Clearly, from both a psychological and biological perspective, children and adolescents experience stress (La Greca et al., 1992). Children and adolescents may experience chronic stressors such as poverty and family conflict, as well as acute stressors such as performance demands associated with school and athletic achievement. In addition, difficulties in peer relations, their own physical growth and identity development, and the presence of a chronic disease may be sources of stress. The sheer number and variety of stress-related questionnaires designed for children and

adolescents underscores that stress is an important and perhaps common phenomenon in this age group (Cohen, Kessler, & Gordon, 1997). That youth have a biological stress response, which may in turn influence disease course, is also supported. For example, adolescents exhibit blood pressure changes in response to laboratory stressors (Ewart & Kolodner, 1991). Such stress-related changes in adolescent blood pressure are predictive of future blood pressure readings (Matthews, Salomon, Brady, & Allen, 2003).

Second, PNI correlational studies provide evidence that youth with chronic disease demonstrate immune system alterations in response to acute laboratory stressors as well as more naturalistic stressors. Studies by Kang and colleagues and Chen and colleagues evaluated the impact of stress on immunity among adolescents with asthma. In studies in which stress was operationalized as an academic exam period (Kang, Coe, Karaszewski, & McCarthy, 1998; Kang, Coe, & McCarthy, 1996; Kang, Coe, McCarthy, & Ershler, 1997a; Kang, Coe, McCarthy, Jarjour et al., 1997b), lymphocyte proliferative response to mitogen increased from baseline to stress, and natural killer cell cytotoxicity decreased from baseline to stress for both subjects with asthma and controls. However, at a poststress assessment, NK cell cytotoxicity continued to remain low in the more severe asthma group, whereas it appeared to be returning to baseline levels in less severe asthmatics and healthy controls. In addition, production of cytokines that promote airway inflammation, particularly interleukin (IL)-5, was lessened in healthy subjects in response to stress, but not in subjects with asthma (Kang et al., 1997b). Results from studies comparing the immune response to stress among adolescents with asthma from different socioeconomic statuses (SES) suggest that SES-related immune differences may be mediated by differences in experiences of stressful life events (Chen, Fisher, Bacharier, & Strunk, 2003; Chen et al., 2006). In addition, perceptions of control may be associated with decreased production of cytokines that promote airway inflammation in asthma (i.e., IL-4, IL-5, and IL-13) and improvement in pulmonary function (Griffin & Chen, 2006). Finally, Sandberg et al. (2000) showed that severely negative life events (e.g., parental separation) increased the risk of an asthma exacerbation 4–6 weeks later; in situations of chronic stress (e.g., school bullying), severely negative events increased the risk of an asthma exacerbation within 2–4 weeks.

Third, many of the same psychological interventions that have been evaluated in adults also are used with children and adolescents, even if in a modified or more developmentally appropriate form (Koeppen, 1974; Powers & Spirito, 1998). For instance, relaxation training and self-hypnosis are routinely used in the treatment of pediatric anxiety (Ollendick & King, 1998) and pain complaints (Holden, Deichmann, & Levy, 1999). Such interventions also may directly influence illness symptoms, such as peak expiratory flow rate in asthma and nausea and vomiting in children and adolescents undergoing cancer chemotherapy (McQuaid & Nassau, 1999). Evidence also suggests that children and adolescents can achieve conscious control over some physiological systems, for instance using biofeedback to increase peripheral temperature in the treatment of pediatric headache (Holden et al., 1999). Developmental factors, such as interest in imaginative play, may make children and adolescents especially good candidates for relaxation and self-hypnotic strategies. If so, such interventions could have pronounced effects on the immune system in pediatric populations.

Fourth, it cannot be assumed that the immune system in developing children and adolescents functions identically to that in adults. Differences between youth and adults have been noted in a variety of biological (e.g., sleep; Owens & Whitmans, 2004) and psychological (e.g., cognition; Piaget, 1952) processes, such that it is not appropriate to conceptualize children and adolescents as being merely small(er) adults. Thus, with respect to the effect of psychological intervention on the immune system, it is plausible that children and adolescents have different immune responses to psychological interventions than do adults.

Finally, children and adolescents are diagnosed with a variety of chronic medical conditions in which the immune system plays a major role. These include asthma (Busse & Lemanske, 2001), inflammatory bowel disease (Bouma & Strober, 2003), insulin-dependent diabetes mellitus (Sia, 2005), juvenile idiopathic arthritis (Sullivan, 2005), lupus (Steinberg et al., 1991), cancer (Greaves, 2006), and HIV (Shearer & Clerici, 1993).

Review of Psychological Interventions to Influence Immune Function in Pediatric Samples

Of the five pediatric studies identified by Miller and Cohen (2001), only two met methodological criteria to be included in their meta-analytic review. Our updated literature search revealed only three additional studies of the influence of psychological treatment on immunity in

pediatric samples. In the interest of commenting on the current state of the literature with pediatric samples, we will critically review all five of the studies identified by Miller and Cohen, as well as the three additional pediatric studies identified in our search. For the critical review, studies are categorized by type of psychological intervention.

Relaxation

Castes et al. (1999) examined the effect of a 6-month psychosocial intervention (PSI) on immunity and health outcomes among children with asthma. Relaxation was a prominent component of the intervention; it is important to note, however, that the entire psychosocial intervention included additional, albeit less described, components such as illness education and self-esteem training. The sample comprised 35 Venezuelan children (ages 6–15 years), 19 of whom were in the intervention. All children received conventional medical care. Youth in the intervention group engaged in relaxation sessions that focused on the formation of mental images of suppression of mast cell degranulation, removal of IgE from these cells, and open airways, all images that are relevant for asthma immunology and symptoms. They had supervised relaxation practice every weekday and were encouraged to use relaxation when they anticipated an asthma episode. The control group did not receive any intervention beyond the conventional medial care. Youth in the intervention group showed a greater reduction in IgE responses to allergen than control children, as well as other immune changes (e.g., an increase in NK cells) that were not observed in the control group. Furthermore, youth in the intervention group had fewer asthma attacks and improved pulmonary function during the intervention compared to 6 months prior to it; no such changes occurred in the control group.

This study suggests that psychosocial intervention may induce immune changes that have an effect on clinical symptoms. There are, however, several shortcomings that limit interpretation of findings. The sample is relatively small, and subjects were not randomly assigned to the intervention and control group; rather, these groups were determined by convenience based on geographical location. Some of the components of the PSI (e.g., education about the allergic response) were not well justified or described, thereby impeding interpretation of the possible role that each component may play in the impact of the intervention. The control group did not receive a similar level of attention as the intervention group. Finally, although the authors describe the influence of PSI on immunity and asthma outcomes, they do not adequately describe the influence of PSI on directly related variables (e.g., subjective relaxation vs. tension). Greater understanding of the effect of PSI on variables that the components of PSI directly target would provide information on the mechanism(s) through which PSI may modulate immune parameters and asthma health outcomes.

Kern-Buell, McGrady, Conran, and Nelson (2000) investigated the impact of biofeedback-assisted relaxation on arousal level, asthma symptomatology, pulmonary function, and immunity among 16 subjects with nonsteroid-dependent asthma aged 13–30 years ($M = 20.5$ years). Participants were randomly assigned to the relaxation treatment group or a wait-list control group. Relaxation training occurred across eight sessions and entailed autogenic relaxation, deep breathing training, and progressive muscle relaxation, with four of the sessions involving biofeedback. Participants in the relaxation group were directed to practice autogenic relaxation via an audio tape twice daily, though adherence to practice was not monitored. Findings included decreased forehead muscle tension, reduced asthma severity and rescue medication use, and improved pulmonary function among treatment participants relative to controls. The intervention group also demonstrated a lower percentage of neutrophils and a higher percentage of basophils than the control group, thereby suggesting less inflammation among treatment participants compared to controls.

Study strengths include a randomized, controlled design; measurement of direct outcomes of treatment; multiple data assessment methods including physiological data and pulmonary function tests; and multiple indicators of immune function. Interpretation of findings is limited by the small sample size and drop-out rate of 25%; only including subjects with mild asthma; the large number of variables under examination relative to the number of participants; and failure to assess adherence to some aspects of treatment (e.g., home practice), thereby hindering understanding of the critical treatment components.

Disclosure

One study of the effects of disclosure on immune function was identified. Sherman, Bonanno, Wiener, and Battles (2000) studied the effects of children and adolescents with HIV ($n = 64$; ages 8–18 years) disclosing their HIV/AIDS status to friends. Controlling for child age and medication, participants who disclosed their HIV+ status to friends during the 1-year study period

(recent disclosers) had a greater increase in CD4+ T-cells percentage, suggesting a slowing of disease progression, than those who disclosed their HIV+ status to friends prior to the study (previous disclosers) or had not disclosed their HIV+ status to friends (nondisclosers).

Strengths of this study include a demographically diverse sample, a relatively high study completion rate, the use of psychometrically sound instruments, and statistical control of potentially confounding variables. One limitation is that participants were exclusively long-term survivors of HIV, over half of whom contracted HIV from blood transfusion and therefore may not be representative of more recently diagnosed children with HIV, most of whom contract HIV from their mother during pregnancy (CDC, 2006). The meaning and benefit of HIV+ disclosure may differ depending on the mode of transmission and the amount of stigma involved.

Hypnosis with Immune Suggestion

Observations of the influence of hypnosis on immunity date back almost 100 years. For example, Clarkson (1937) described a case study of the effect of hypnosis on an 18-year-old girl with asthma and an allergic reaction to egg. Under 30 min of hypnosis with repeated suggestion for no allergic reaction to occur, she did not have an allergic response to egg presentation. The next day, without the hypnotic intervention, she demonstrated an allergic reaction to egg that was comparable to her allergic reaction at baseline. These early observations suggested that hypnosis may influence immunity, as allergic responses are immune-mediated.

This study is strengthened by studying both the impact of hypnosis and the impact of its removal, thereby lending greater support to the idea that hypnosis caused the reduced allergic response. A limitation of the study is that the effect was demonstrated in only one case with limited demographic, medical, and psychological (e.g., hypnotic susceptibility) information.

Olness, Culbert, and Uden (1989) conducted a prospective, controlled study examining the effect of self-hypnosis on sIgA in saliva. Fifty-seven children were randomly assigned to either: (a) self-hypnosis (group A); (b) self-hypnosis with specific suggestion to increase saliva immunoglobulins (group B); or (c) an attention (no-treatment) control group (group C). Hypnotic susceptibility was comparable across groups. At session 1, all children watched a videotape on the immune system and listened to a general relaxation tape that included imagery. Two weeks later, at session 2, group A listened to a self-hypnosis tape, group B listened to the same tape, and was given specific suggestion to increase saliva immnunoglobulins, and group C conversed with research assistants for the same amount of time that group A and B received treatment. Salivary levels of sIgA did not change for any children between baseline and the start of session 2. During session 2, however, only group B (those subjects given specific suggestion to increase salivary immunoglobulins) demonstrated an increase in salivary sIgA.

Study strengths include a prospective, randomized, and controlled experimental design. One limitation is that the children had difficulty attending to the relaxation and immune system videotape at session 1, thereby making the influence of these components on salivary sIgA levels unclear. Although, the authors report that there was no association between children's self-reported interest level and salivary sIgA, children's self-reported interest level may have been influenced by social desirability. Another drawback is the lack of descriptive information about the sample (e.g., child race/ethnicity, socioeconomic status, and medical history), which raises questions about external validity. Lastly, although mean outcome scores for the groups are reported, standard deviations are not, thus preventing calculations of treatment effect size.

Conditioning

One case study examined the influence of conditioning on an adolescent female with severe lupus erythematosus (Olness & Ader, 1992). The conditioning procedure involved pairing cyclophosphamide (CY) therapy for lupus with cod liver oil and rose perfume monthly for 3 months. Subsequently, cod liver oil and rose perfume were offered monthly, whereas CY treatments were offered every other month. Over a year, the patient only received half of the CY dose that otherwise would have been administered for her condition. She improved clinically, as evidenced by disease markers and hospitalization rate, as one might have expected had she been given the full-dose regimen of CY. Cod liver oil and rose perfume were presented to the patient for another 3 months; however, after 3 months, she stopped the cod liver oil due to nausea. She reportedly continued to imagine a rose and was noted to being doing well 5-years later.

Olness and Ader (1992) applied findings regarding conditioned pharmacotherapeutic effects on autoimmune disease in animals (Ader & Cohen, 1982) to people with autoimmune problems. One limitation of study of Olness and Ader (1992) is that the influence of the conditioned stimuli (i.e., cod liver oil and rose perfume) is

confounded with the influence of a half-dose regimen of CY. Consequently, it is unclear whether the improvements in the patient's lupus after the yearlong conditioning procedure are due to a conditioning effect, a half-dose of CY, or a combination of the two. Interpretation of the follow-up data also is difficult, because it is unclear whether or not the patient continued to receive CY therapy on either a half-dose or full-dose regimen. The study also is limited by the fact that the results were demonstrated in a single individual with very little demographic information reported.

Combination treatments

Hewson-Bower and Drummond (1996) conducted a study examining the effect of relaxation alone versus relaxation with immune suggestion on salivary sIgA in children with and without recurrent respiratory infection. The sample included 90 Australian children aged 8–12 years, 45 of whom had had 10 or more upper respiratory tract infections (URTIs) in the previous year and 45 of whom had had no more than two URTIs in the past year. Children were randomly assigned to one of three conditions: relaxation alone, relaxation with suggestion to increase immune system proteins, or attention control. All children watched the same immune function video described in Olness et al. (1989). Afterward, children in the relaxation condition were encouraged to do progressive muscle relaxation and imagery, whereas children in the relaxation with immune suggestion condition engaged in these relaxation techniques with additional instructions to make more immune proteins in their saliva. Children in the control condition talked with the experimenter. Concentrations of salivary sIgA increased in the two treatment conditions, but not in the control condition. The salivary sIgA/albumin ratio, a more specific indicator of local mucosal immunity, however, was greater among youth who received relaxation with suggestion than among youth who received relaxation alone. Interestingly, healthy children and those with recurrent URTIs did not differ in the amount of change in salivary sIgA and the salivary IgA/albumin ratio. The authors concluded that disruptions in mucosal immunity in children with recurrent colds and flu, as illustrated by low salivary sIgA/albumin ratios at baseline, did not hamper the salivary sIgA response during relaxation and relaxation/hypnosis with immune suggestion and, thus, that psychological interventions may have therapeutic value for these children.

Strengths of this study include a randomized and controlled experimental design, a substantial sample size, and appropriate statistical control for some variables. The authors also improve upon the study by Olness et al. (1989) by measuring subjective ratings of relaxation following the two interventions. Objective measures of relaxation, such as physiological indicators, would address some of the limitations of self-report. Another concern is that the number of children with URTIs who also had a history of allergies, an immune-mediated condition, was greater than the number of healthy children with a history of allergies, thereby suggesting an important group difference in immune function at baseline that was not statistically controlled. Finally, an effect size cannot be calculated because standard deviations of outcome scores by group are not provided.

In a 2001 study, Hewson-Bower and Drummond examined the impact of stress management versus guided imagery on URTIs, mucosal immunity (i.e., salivary sIgA), and psychological functioning among 45 children aged 8–12 years ($M = 9.4$ years) with 10 or more URTIs over the past year. Participants were randomly assigned to one of two treatment conditions or to a wait-list control. Participants in both treatments underwent four training sessions and 13 weekly group therapy sessions, the latter to practice skills. The youth also were given daily homework specific to their treatment. The stress management intervention involved emotional expression, problem solving, progressive muscle relaxation, and positive nonspecific imagery, whereas the guided imagery intervention entailed guided imagery with specific suggestions to increase immune proteins and be in control, relaxed breathing, and positive, nonspecific imagery. There were no differences between the treatment and wait-list control conditions in the number of symptomatic episodes over a 13-week period; both treatment conditions, however, had shorter episodes than the control condition, with participants in the stress management treatment having the shortest episodes of all. Participants in the stress management and guided imagery group, but not the control group, also experienced benefits in psychological functioning (e.g., mood), with stress management participants experiencing the most benefits over the course of treatment. Furthermore, salivary sIgA levels were bolstered in both treatment groups with no difference between the treatment groups when controlling for baseline levels.

In a replication study reported in the same article (Hewson-Bower & Drummond, 2001), 28 8 to 12-year-old children were randomly assigned to either a combination treatment of stress management and guided imagery or to a wait-list control. Initial treatment

(during which skills were taught and practiced) occurred in small groups weekly across 4 weeks. For an additional 8 weeks, all participants monitored cold and flu symptoms with parental supervision. Treatment participants also completed daily homework assignments plus weekly group meetings. Results indicated decreased frequency and duration of symptomatic episodes among the treatment group, but not among the control group. Furthermore, psychological functioning improved and salivary sIgA during symptom-free periods increased in the treatment group. At 1-year follow-up, at which point those in the treatment group monitored cold and flu symptoms for 8 weeks and completed measures of psychological functioning, frequency of cold and flu episodes returned to baseline levels but continued to be of shorter duration than at baseline. Most improvements in psychological functioning also were maintained.

Strengths of set of experiments of Hewson-Bower and Drummond (2001) include randomized, controlled designs, well-described treatment components, assessment of treatment adherence (e.g., parental monitoring of child homework completion), measurement of direct outcomes of treatment, replication of an initial study, and the inclusion of follow-up data in the replication study. This research is limited, however, by relatively small samples, lack of demographic information regarding the samples, built-in expectancy effects (i.e., participants were told that the treatment would decrease colds and flu), relying on self-report of symptomatic episodes that may have been biased because participants knew the purpose of the study, and including only one immune outcome measure.

Child Literature: Summary of Critique and Relevant Recommendations

Research examining the influence of psychological interventions on immunity in children suggests many intriguing findings, such as the possibility that psychological interventions induce immune changes that influence clinical outcomes. As such, immunological measures tap into an important part of overall child well-being and can enhance our understanding of the effect of psychological intervention on disease course. To improve upon our current knowledge base, a number of methodological shortcomings should be addressed in future research. Common limitations of the current literature include nonrandomized, controlled studies; small, homogeneous samples; selection bias; poorly described samples and methods; lack of multiple informants and methods; presence of confounding variables, uncontrolled for statistically, or by participant selection; and inability to calculate treatment effect sizes due to study design and data reporting limitations.

In addition to addressing these limitations, a few recommendations thought to be particularly key to enhancing our understanding of the influence of psychological interventions on immune outcomes include describing and justifying each component of multicomponent interventions to assist with interpretation of findings, measuring treatment integrity and adherence to treatment, evaluating outcomes directly targeted by interventions, and measuring multiple indicators immune function. Taking these steps greatly would improve upon the existing literature and help establish a highly important area of research that is relatively untapped to date.

Challenges, Opportunities, and Future Directions

There are several challenges for conducting research on the effect of psychological interventions on immunity in pediatric samples, but addressing these challenges also opens significant opportunities for pediatric psychologists. Salient challenges include: establishing collaborative relationships with clinical immunologists; choosing immune markers that are detectable, reliable, interpretable, cost-effective, sensitive to psychological change, and relevant to disease progression; recruiting adequate samples of children; gaining parental consent and child assent to blood draws; and conducting blood draws without causing undue distress.

Pediatric psychologists are positioned well to meet these challenges. First, because of experience providing clinical service and conducting research in medical settings, pediatric psychologists are familiar with developing clinical and research collaborations with medical providers (Drotar, 1995) and with attending to medical aspects of their patients with pediatric disease. The same skills used to develop collaborations with medical providers should be used to develop collaborations with clinical immunologists who have expertise in immunological methods and interest in the effect of immunity on health. Collaborations could be with those who have specific interest in the immunological aspects of the population being studied (e.g., immunology of pediatric asthma) or in the influence of psychological processes (e.g., stress and depression) on the immune system. The clinical immunologist can provide expert

recommendations regarding appropriate immune markers (i.e., those that are related to the disease being studied and/or those likely to change given the intervention being employed) and methods (e.g., enumerative and/or functional).

Second, because of consultative relationships with hospital-based pediatricians and subspecialists, pediatric psychologists have the potential to recruit larger samples of pediatric patients with a variety of diseases in which the immune system plays an integral role. Because the clinical management of some of these diseases (e.g., inflammatory bowel disease) includes recurrent blood work, these consultative relationships enhance the possibility of integrating research protocols into clinical encounters and, thus, the possibility of obtaining blood samples for research in the context clinical encounters without requiring additional needle sticks. In fact, during the consent process researchers should clearly describe the method for obtaining blood samples (e.g., whether or not blood will be drawn as an additional sample during a clinical encounter during which blood is already being drawn). Importantly, pediatric psychologists are experienced with medical and psychological methods to reduce distress associated with medical procedures, including blood draws (Blount, Piira, Cohen, & Cheng, 2006). Numbing creams and/or pain and anxiety management techniques should be used to decrease fear and distress associated with blood draws.

Given the challenges and financial costs involved in integrating assessments of immunity into studies of psychological interventions with pediatric samples, pediatric psychologists should be judicious with respect to when to integrate such measures. The following strategies are recommended as potential starting points. First, immune assessments may focus on particular populations for whom the immune system plays an active role in the ongoing underlying pathophysiology of the disease (e.g., asthma and inflammatory bowel disease) and in populations in which the link between stress and immune change has been studied to a greater extent. Second, research could focus on those pediatric patients living in, or through, more stressful experiences (e.g., poverty, divorce, and bereavement), including during critical periods of disease course (e.g., diagnosis, hospitalization, and important change in treatment), and developmental transitions. Third, because direct intervention-related changes in immunity are likely to result from changes in the underlying biological stress system, initial research may focus on interventions (e.g., stress management) aimed at altering the stress system. Special attention should be paid to clearly describing treatment components and to measuring outcomes directly targeted by interventions such as the degree of relaxation following a relaxation intervention; this will not only provide data on the effect of the intervention, but also will help to elucidate mediators of immune change. Attending to these recommendations will enhance the cost-effectiveness of PNI intervention research in pediatric samples, improve greatly upon the existing literature, and help establish a highly important area of research that is relatively untapped to date.

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