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Cognitions, Emotions and Immune Response : An Attributional Model for the Mind-body Connection

Byron Earle Greenberg

LOMA LINDA UNIVERSITY

Graduate School

COGNITIONS EMOTIONS AND IMMUNE RESPONSE: AN ATTRIBUTIONAL MODEL FOR THE MIND-BODY CONNECTION.

by

Byron Greenberg

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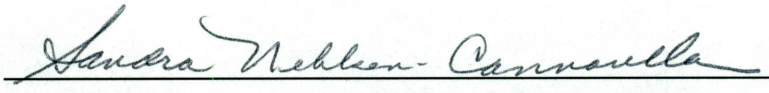
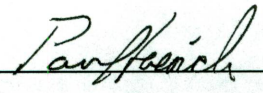
Each person whose signature appears below certifies that this thesis in their opinion is adequate, in scope and quality, as a thesis for the degree Masters of Arts.

,Chairperson

Hector Betancourt, Professor of Psychology



Sandra Nehlsen-Cannarella, Professor of Immunology



Paul Haerich, Associate Professor of Psychology

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Over the past twenty years there has been renewed interest in the mind-body connection. Meyers (1992) suggested that there are three general categories of research in the field: 1) correlational studies relating psychological factors and physiological effects (e.g., effects of personality on relaxation or motivation on exercise), 2) correlational studies relating psychological events and biomolecular effects (e.g., decreased cytotoxic function of cells after experiencing a stressor), and 3) mind-body interactions at the cellular level (e.g., interfacing and cross-talk between nervous, endocrine and immune cells).

A main concern with current research is the lack of theoretical support and empirical control for the psychological factors measured and reported. For instance, some contemporary stress measures utilize specific events (or stressors) as the scale for individual stress level and do not distinguish adequately between stress, distress, anxiety and other emotional states. Cohen, Tyrrell, and Smith (1993) comment on the disparate and inconsistent definitions of stress as well as the disagreement on how stress should be measured across disciplines. In psychoneuroimmunology, this may be due in part to the fact that "most of the experimental work has been conducted with animals and indicates that a variety of behavioral manipulations or stressors can influence susceptibility to a variety of disease states in a variety of species" (Ader and Cohen, 1993, pg. 64). Thus, animal models have set the stage for research with human subjects and perhaps influenced design and theoretical assumptions about the equivalence of stress and stressors. A large portion of the literature makes this assumption, as exemplified in a

study by Kiecolt-Glaser, Fisher, Ogrocki, Stout, Speicher, and Glaser, (1987) who use marital problems as the stress-determinant in the relationship between stress and immune functions. Human studies such as this, then seek to assign uncontrolled variance to individual differences and error variance (Manuck, 1991; Moore and Strauss, 1987), ignoring critical and potentially manipulatible cognitive components as latent sources of both controlled and uncontrolled variance. This theoretical approach neglects those higher cortical functions particular to the human species; functions that have repeatedly been shown to affect stress level. For the purpose of this study, stress will be defined as those emotional states related to events which exceed or seriously challenge coping ability.

The literature demonstrates a path between stress-emotions and immune response (Glaser, Kiecolt-Glaser, Stout, Tarr, Speicher, and Holliday, 1985a; Landman, Muller, Perini, Wesp, Erne, and Buhler, 1984; Naliboff, Benton, Solomon, Morley, Fahey, Bloom, Makinodan, and Gilmore, 1991; Mouton, Fillion, Tawadros, and Tessier, 1989; Glaser, Kennedy, Lafuse, Bonneau, Speicher, Holliday, and Kiecolt-Glaser, 1990). Attribution theory suggests a directional link between cognitions and emotions (Weiner, 1982a, 1982b, 1985, 1986, 1993, 1995; Betancourt, 1990, 1992). To date, much of the psychoneuroimmunologic stress research has assigned stress level as a function of the number of stressors to which a person is exposed. This approach is behavioral in nature and does not account for the interpretation of the stressor by the individual who is experiencing the stress. Amirkhan (1991) points to the

25+ percent of concentration camp survivors who, despite exposure to chronic and traumatic stressors, do not show psychiatric or physical disease. He goes on to state, "individual differences in the perception of the stressor... seem to ameliorate or exacerbate its impact on the person" (pg. 79-80). Psychoneuroimmunologic research suggests a role for cognitions in the process but do not adequately operationalize the role of those cognitions within the psycho-neuro-immuno-triarchy.

Attribution theory proposes that cognitions precede emotional states (Weiner, 1985; Betancourt, 1990, 1992). Attributional research on emotions has focused primarily on the cognitive intermediary variables involved in subjective states. The theoretical model proposed in this study suggests that cognitions come before immune-relevant stress-emotions, potentiating a psychologically malleable link in the immune system. Thus, the authors seek to test the proposition that cognitive (attributional) processes account for variance in emotional states which in turn mediate innate and adaptive immune responses.

Wiedermann (1988) contends that the idea that emotional disturbance may trigger physical illness (e.g., the increased likelihood that a person's death might follow that of a spouse) is not new and that such phenomena are currently explained in terms of disturbances to the immune system by specific communication and interactions between nervous, immune, and endocrine systems. One neglected aspect of this and other models is the role of cognitions as possible mediational variables in the activity of the nervous system, and just as importantly, the consequential affect-related outcomes.

Felten, Cohen, Ader, Felten, Carlson, and Roszman (1991) state "the consensus ...is that the anterior hypothalamus is involved, either directly or indirectly, in the stimulation of both humoral and cell-mediated immune functions." pg. 7. This suggestion is significant in light of other roles of the hypothalamus such as drives and emotions in humans (Sandner, Oberling, Silveira, Di-Scala, et al, 1993; Rolls, 1990; Simonov, 1982, 1984; Nakao, 1979), which have been related directionally to attributions and appraisals (Weiner, 1987; Smith and Lazarus, 1993). Felten et. al. (1991) suggests this relationship is strengthened by lesion research, in which physical manipulation of the anterior hypothalamus resulted in significant decreases in antibody production (Tyrey and Nalbandov, 1972), decreased in natural killer (NK) cell activity (Cross, Brooks, Roszman, and Markesbery, 1984), decreases in nucleated spleen cells and thymocytes (Brooks, Cross, Roszman, and Markesbery, 1982; Katayama, Kobayashi, Kuramoto, and Yokoyama, 1987), and other immune-compromising anomalies. Further, research has shown that a direct path from the brain to the immune system may be accounted for by the hypothalamic-pituitary-adrenal (HPA) axis. In this pathway the hypothalamus releases corticotropin-releasing factor which induces the anterior pituitary to release adrenocorticotropin (ACTH) and Beta-endorphin. ACTH acts on the adrenal gland which releases glucocorticoids; while in small amounts are necessary for normal immune functioning, relatively high amounts of these hormones have a negative effects. (For a review of these findings, see U.S. Department of Health and Human Services: National Institutes of Mental Health, 1994)

Another related and promising line of research is based on the findings of researchers such as Bulloch (1985) and Felten, Felten, Bellinger, Carlson, Ackerman, Madden, Olschowski and Livnat (1987) who first discovered direct innervation of primary and secondary lymph tissue, and exposed the impact of neurotransmitters on lymphocytes, respectively. It may stand to reason that variations in hypothalamic status due to cognitive-emotional activity could impact that portion of the autonomic nervous system which effects the lymph tissue. This, combined with a growing understanding of the autonomic nervous system's role in the innervation of lymph tissue, may demonstrate a major source of immunologic manipulation and management by the brain's physiological response to cognitive processes.

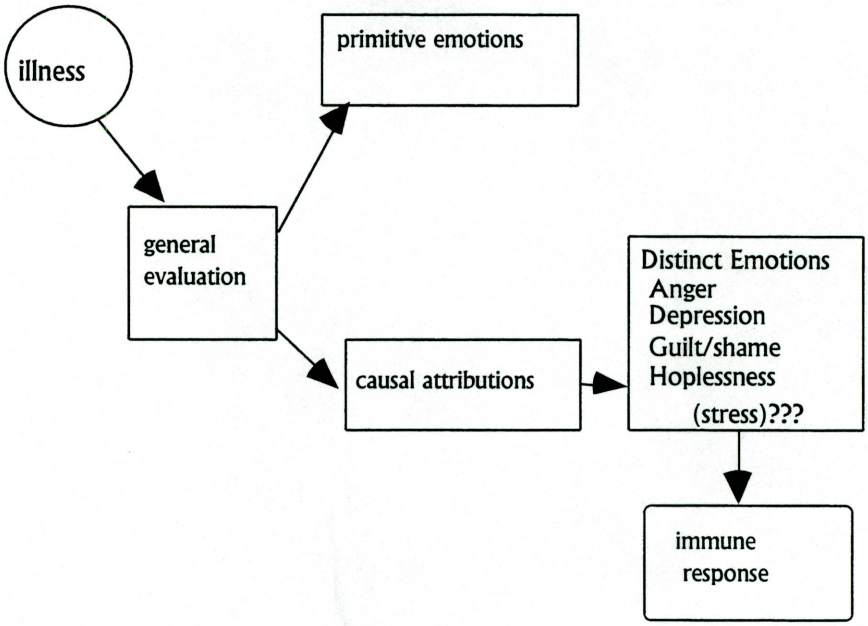
Stress research has made major efforts toward synthesizing an inclusive paradigm which could bring together emotions and immune responses. However, Van Rood, Bogaards, Goulmy, and Van Houwelinen, (1993) showed inconsistencies in the results of studies included in a meta-analytic analysis of stress-immune relations. Several problems with methodology were evident, including differing immunological techniques which have been shown to account for much of the variance in immune and other response measurements (Schleifer, Keller, Bond, Cohen, and Stein, 1989). Differences in stress type are also noteworthy. Kemeny, Solomon, Morley and Herbert (1991) state:

> "There have been no human studies comparing the effects of acute and chronic stressors in the same individual. However, the long-term effects of chronic stressors and the immediate effects of acute

> stressors have been evaluated in separate studies. These reports suggest that chronic stressors may 'depress' certain immune processes while there may be an immediate enhancement to acute stressors" (pg. 574).

According to the proposed model (see Figure 1), these findings reflect the difference between the primary emotional responses (reflexive) and secondary (i.e. attribution-dependent) responses which are longer lasting and potentially more exhausting to the system. This conceptual difference may account for some of the inconsistencies in immune responses to stress reported in the literature. Other issues include using appropriate measurements to define the stress state, procedures used to define the immune response, and most important to this study, measures of individual differences in perception and interpretation of controllability of the stressor.

Figure 1. Modification of the Weiner Model



Stress can be defined as an experiential state in which demands imposed by events exceed ability to cope (Cox, 1976; Lazarus and Folkman, 1984). Research has demonstrated a relationship between mental stress and the immune system, (Glaser, Kiecolt-Glaser, Stout, Tarr, Speicher, and Holliday, 1985a; Landman, Muller, Perini, Wesp, Erne, and Buhler, 1984; Naliboff, Benton, Solomon, Morley, Fahey, Bloom, Makinodan, and Gilmore, 1991; Mouton, Fillion, Tawadros, and Tessier, 1989; Glaser, Kennedy, Lafuse, Bonneau, Speicher, Holliday, and Kiecolt-Glaser, 1990). A partial list of stressors which have been linked to immunocompetence include: sleep deprivation (Palmblad, Petrini, Wasserman, and Akerstedt, 1979), unemployment (Arnetz, Wasserman, Petrini, Brenner, Levi, Eneroth, Salovaara, Hjelm, Salovaara,

Theorell and Petterson, 1987), bereavement (Bartrop, Lazarus, Luckhurst, Kiloh, and Penny, 1977; Schleifer, Keller, Cammerino, Thornton and Stein; 1983), divorce and separation (Kiecolt-Glaser, Fisher et al, 1987), long-term care of patients with Alzheimer's disease (Kiecolt-Glaser, Glaser et al., 1987), natural disasters (Schaeffer, McKinnon, Baum, Reynolds, Rikli, Davidson, and Fleming, 1985), and exhaustive exercise (Nieman and Nehlsen-Cannarella, 1994).

The intensity and duration of stressors such as these may be regulated by the cognitive processes associated with them. In fact, Oliver and Bock (1990) demonstrate the use of rational emotive therapy, a cognitively-based therapeutic process, to lower stress among long-term care-givers of patients with Alzheimer's disease. Kemeny, Solomon, Morley and Herbert (1991) cite Laudenslager and Ryan (1983) and Shavit et al., (1983) and suggest that perceived "controllability" of a stressor may be viewed as an analog for the coping process in humans and may be critically related to immune response. Levy, Herbermann, Lippman, d'Angelo and Lee (1991) shows that social support and emotional distress were associated with the rate of disease progression in cancer patients. Hall et al. (1994) suggest that behavioral interventions may be effective because they elicit a sense of control over events. This supports the proposed model and may provide a plausible understanding of the yet unexplained placebo effect. Hence, it may be determined that cognitive intermediary processes regulate immune response to stress by regulating the emotional impact of stressors.

Attribution theory, as described by Weiner (1982a, 1982b, 1985, 1986, 1993, 1995), suggests that the innate quality of the stressor does not cause an emotional state; rather, it is the individual's interpretation of the stressor--the cognitions related to the stressor--which cause an affective response. Weiner's attributional model includes three main causal components (Locus, Stability and Controllability) which are especially relevant to the attribution-emotion process. Locus relates to the internality or externality of an event or circumstance. For instance, among cancer patients, the person whose cancer was caused by smoking may see the cancer as having internal causes. If, on the other hand, it is related to being exposed to toxins at work, external causality may be ascribed. Controllability is another attributional determinant of causality. The person who gets cancer because they worked with toxins may have been unaware of the risk and, thus, see themselves as having had no control over their fate. On the other hand, the person who smoked, having read the warnings on the package, may see the event as having been controllable. Stability is the third attribution in Weiner's model. A person who has cancer may feel that the disease is stable and will run its life-ending course regardless of intervention. Another may interpret the illness as unstable in the face of chemo- or radio- treatment.

Weiner (1985) proposes that a general outcome will elicit a "primitive emotion" (pg. 560). This emotion-state is reactive and relies primarily on a reflexive beneficial or harmful appraisal process. "Following outcome appraisal and the immediate affective reaction, a causal ascription will be sought. A different set of emotions is then generated by

the chosen attribution(s)" pg. 560. These emotions are what Weiner terms "attribution dependent." Cox (1978) states that stress is usually reported or "described in ways associated with emotions such as anger, anxiety, depression, fear, grief, guilt, jealousy and shame " (pg. 27). These negatively toned emotions are what Lazarus (1976) terms 'stress-emotions', and are related to stressors. Not all emotions are stress-related emotions, however; those emotions which are related to stress appear to be fertile ground for plumbing stress level.

Weiner (1985) proposes that causal ascription and expectancy change are linked. Hall, Anderson and O'Grady (1994) suggest that expectations play a critical role in stress/immune modification. Thus, the theme of hope or hopelessness for the medical patient appears to be related to causal ascriptions precipitating expectations of alterable or unalterable negative outcomes. If there is no chance of change in condition (stable, uncontrollable), then hope may be lost. This is supported by the literature on hopelessness, and may be related to attributions of globality (Weiner, 1985). Further, hope may be shown to affect motivation which could have a bi-directional effect on the attributional process because of its impact on effort. The literature shows that there is substantial impact of social support as a coping mechanism involved in emotional status (Levy, et al, 1991; Solomon, Temoshok, O'Leary, and Zich, 1987; Geiser, 1989; Thomas, Goodwin, and Goodwin, 1985; Kiecolt-Glaser et al., 1987), however, it should be noted that those who feel helpless may use avoident coping styles, isolating themselves

from critical support. If so, this would support the bi-directional relationship between emotions and behavior.

In conclusion, the literature shows a clear path between stress-emotions and immune response. Attribution theory suggests a directional link between cognitions and emotions. To date, much of the stress research has assigned stress level as a function of the number of stressors to which a person is exposed. This approach is behavioral in nature, and does not account for the interpretation of the stressor by the individual who is experiencing the stress. The literature suggests a role for cognitions in the process but does not adequately operationalize the role of those cognitions within the psycho-neuro-immune-triarchy. The proposed theoretical model (see figure 1) suggests that cognitions come before immune-relevant stress-emotions, potentiating a psychologically malleable link in the immunologic system.

It is the purpose of this study to propose and test a model which examines the role of cognitive (attributional) processes or mediating variables in the stress immune response process. Four main hypotheses will be tested in light of a proposed model: 1) There is a significant difference in immune response as measured by assays of innate (natural killer and phagocytic cells), and adaptive (lymphocyte subsets) immunity between those who are in a high stress category versus low stress category. 2) Stress-emotional states will be a function of attributional thinking associated with the course and nature of a primary stressor. 3) Attribution will influence the immune response through the mediating role

of stress-emotion responses. 4) Negative emotions such as anxiety, anger and depression will negatively influence immune response.

Methods

Subjects

Fourty-six parents, whose children were admitted to the pediatric intensive care unit at Loma Linda University Medical Center, were selected by approaching those who were visiting the unit on Thursday and Friday mornings. An anchor group of fourteen subjects were chosen from personnel (i.e. unit secretaries, social worker, stock personnel and experimenters) on the same unit, excluding doctors and nurses. The rationale for including this group relates to literature which suggests that events determine stress level. This would indicate that all parents experiencing the stress of having a child on the pediatric intensive care unit, would have high stress levels. Including a group who did not have this stressor (staff on the unit) was intended to allow for a low stress comparison group. Choosing staff on the same unit is an effort to control for potential contagions that parents may encounter while spending time with their children. This prevents any airborne contagion(s) on the unit from creating additional variance in immune markers. The study was run over a three-month period. Husbands and wives were selected in pairs when possible. Participants were presented with the opportunity to participate or decline which may have introduced an element of self-selection.

This self selection method may introduce additional error variance; however, ethical parameters would prevent mandatory participation in

such a study. Further, by randomizing as much as possible and including a randomized control group, chance of type I errors was reduced.

Instruments

Psychosocial Instrument

An instrument containing scales reflecting subjective reports of stress-emotion levels, current attributional processes, and coping styles was administered.

Emotions such as tension-anxiety, anger-hostility and depression-dejection were measured using the short form of the Profile of Mood States survey (POMS; McNair, Lorr, and Droppleman, 1971). Internal consistencies for these susbscales range from 0.87 to 0.95 on groups ranging from individuals in outpatient mental health units to college students (McNair et al., 1971). This instrument consisted of thirty adjectives followed by a 0-4 scale: (0 = not at all, 1=a little, 2=moderately, 3=quite a bit and 4=extremely). The subject received written instructions to mark the response which best indicated how they have been feeling during the past week. Hopelessness was measured using the twelve-question Hope scale (Snyder, 1991). Attributions were assessed using the question:

> "Many times people find themselves faced with stressful life events. Please write a couple of paragraphs describing your most recent stressful event, detailing the situation itself and leaving out the specifics of what happened before and after. Then answer the following twelve questions, keeping in mind that they refer to your

answer in this question. You may use the back of this page if necessary."

followed by a 12-question Attribution scale called the Causal Dimension Scale (CDSII; McAuley, Duncan, and Russell, 1992). This 12-question instrument included subscale questions which measured four primary properties of causal attributions: (1) externality/internality, (2) stability, (3) controllability by self, and (4) controllability by others. Each of these four subscales consisted of three questions presented in a 5 point likert type arrangement. For instance, "controllability-by-self" included the questions: Is the cause(s) of what you wrote above something...: (c-3) "manageable by you - not manageable by you?", with 5 being completely manageable by the subject and a 1 being completely unmanageable by them ; (c-5) "you can regulate - you can not regulate?" , with 5 being completely regulatory and 1 being unregulated; (c-11) "Over which you have power-over which you have no power", with 5 being completely within the power of the subject and 1 being completely outside the power of the subject.

Demographic information included questions on: general health status, age, gender, occupation, education level, religious affiliation, ethnicity, marital status, diagnosis of hospitalized child, socioeconomic status, and number of children in the home was also obtained (Kerlinger, 1993). A measure of coping styles was utilized to control for ability to cope as another index of stress and stress behavior (Amirkhan, 1993). This instrument along with the helplessness scale were collected for use in a future analysis.

Immunologic Instruments

Innate Immune Measures

A battery of tests were run to catch expected changes in phagocytic cell and natural killer cell function and complete blood cell counts (CBC). These assays were used because of their ability to measure functional as well as numerical aspects of total immune competence (Van Rood, et al., 1993; Cohen et al. 1993). The CBC was performed in the clinical lab. The following procedures were used for the phagocytosis, respiratory burst and natural killer cell function assays.

Phagocytosis and Respiratory Burst Assay

The phagocytosis utilized a FITC-labeled bacteria *(Staphylococcus aureus;* Molecular Probes, Eugene, OR) to quantify the degree of phagocytosis by granulocytes and monocytes. To determine the extent of respiratory burst exhibited by granulocytes and monocytes, 2',7'-dichlorodihydrofluorescein diacetate (DCF-DA; Molecular Probes) was employed, a non-fluorescent molecule which is oxidized to green fluorescent dichlorofluorescein (DCF) by oxygen radicals are generated in the respiratory burst to kill unlabeled *Staphylococcus aureus.* The white blood cell count was acquired using the Becton Dickinson Unopet manual counting protocol. Using two-color flow cytometric immunophenotying (CD45-FITC/CD13,14-PE), the monocyte and granulocyte percentages were determined. Bioparticle reagents of unlabeled and labeled *Staphylococcus aureus* were suspended into phosphate-buffered saline solution at a working concentration of 3×10^5 bioparticles/mL. After determining the number of phagocytic cells in 100 mL whole blood, and

adding 15 FITC-labeled bacteria per cell, the mean channel fluorescence (FITC) were analyzed to determine the degree of engulfed bacteria (non-phagocytized bacteria were quenched with ethidium bromide, final concentration of 200 mM). To determine the respiratory burst activities, either DCF-DA (final concentration, 100 mM) (for quantifying basal activity level), or DCF-DA and unlabeled bacteria (stimulated activity level) were added to 100 mL whole blood. After incubating the samples for 60 min (37°C) in the dark, lysing the red blood cell (RBC), centrifuging, and resuspending the cell pellets, samples were acquired on the flow cytometer. For each sample, 10,000 phagocytes (monocytes and granulocytes) were acquired. Monocyte and granulocyte populations were analyzed individually for the extent of their phagocytosis and respiratory burst.

Natural Killer Cell Assays

Natural Killer cell assays (Chang, Gusewitch, Chritton, Folz, Lebeck and Nehlsen-Cannarella, 1993) were also performed. The first portion of this process involved target cell labeling. An appropriate number of K562 target cells ($5x10^4$ for each person tested) were washed and resuspended in phosphate-buffered saline solution at a concentration of $1x\ 10^6$ cells/ml. Following the dispensing of 10 µL of 3 mM DiO (3,3'-dioctadecyloxacarbocyanine perchlorate) working solution into individual Falcon 12x75 polystyrene culture tubes (Becton Dickinson Labware), 1 ml of the target cell suspension will be added forcefully to disperse the dye. The tubes were incubated for 20 min at 37 degrees Celsius in 5% CO_2, followed by two washes with phosphate-buffered

saline solution and resuspension in complete medium at a concentration of $1x10^6$ cells/ml.

Effector cells were added to each of five Falcon polystyrene 12 x 75 assay tubes to yield effector-target ratios of 40 : 1, 20 : 1, 10 : 1, 5 : 1, and an effector-cells-only control tube. Cells will be pelleted and resuspended in a standard volume of 130 ml with complete medium. DiO stained target cells (10µl = $1 x10^4$ cells) were added to each of the effector:target ratio tubes and to a separate target background control tube. Propidium iodide working solution (130 µl/ tube) was then added into each of the tubes followed by centrifugation at 1000 x *g* for 30 seconds in a Serofuge (Clay Adams, Parsippany, NJ) and incubation at 37 degrees Celsius in a 5% CO_2 incubator for 2 hours. At the end of the incubation, cells will be dislodged by gentle mixing followed by 2-3 s of vortexing just before flow cytometric analysis.

Results from the assay were used to formulate a mathematical index (Lytic Units) which provides an indication of how many times the subjects natural killer cells can successfully kill 20% of the challenger, in this case K562 target cells. This number was further reduced such that subjects who had 1-50 lytic units were assigned a score of 1, subjects with 51-100 lytic units were assigned a score of 2, up to those who had 951-1000 lytic units in which case they were assigned a score of 20.

Adaptive Immune Measures

Changes in both cell numbers and function may occur. Hence, we measured cell sub-populations (percentages and absolute numbers), and their products and functional affects such as Natural killer cytotoxisity and

phagocytic ability. This provided the functional assays with a percentage-of-total-cell-population basis.

Procedure

Starting December 10, 1995, parents of patients admitted to the pediatric intensive care unit at Loma Linda University Medical Center were approached by the primary investigator and asked if they would be willing to participate in a study aimed at helping those who are experiencing the stress of family illness. The experimentor approached those parents whose child had been admitted a minimum of 48 hours before being contacted to participate. For each person who declined to participate, the next admittee's parents were asked until the 60 total participants were acquired including anchor group members.

The primary investigator gave the participants an explanation of the study objective and components, and an opportunity to have questions about the study answered. Next, each participant was provided with the California experimental subjects bill of rights and an informed consent as approved by the LLUMC Institutional Review Board. They were then taken to a room on the unit were a sample of blood was drawn. The same hospital phlebotomist performed the venipuncture each time. Following the blood draw, the subjects were returned to their child's room and asked to complete a survey. This standardized procedure was designed to prevent the child from experiencing stress relative to their parents discomfort and visa versa. Returning the parent to the room to fill out the survey allowed the parents to be in contact and experientially aware of the stressfull event.

All of the blood was drawn before the survey was administered; both blood and survey were gathered between the hours of 9 a.m. and 12 noon. Coded identification labels containing a unique identification number for each person were used to label the survey, the blood specimen collection, and the immune profile worksheet. Blood samples were processed within 3 hours of venipuncture. Both serum and plasma were frozen and banked for future studies.

Results

A preliminary analysis was performed to assess the validity of the instruments being used. Factor analysis performed on the attribution instrument revealed that the cognitive factors loaded as anticipated. Three primary factors representing Factor 1, controllable-by-self; Factor 2, control-by-others; and Factor 3, stability of situation, emerged and are shown in Table 1.

Table 1: Factor analysis of Attribution variables

and Factor Correlation Matrix

Variable	Factor 1	Factor2	Factor 3	Factor 4
C2	0.60	0.00	0.12	**-0.03**
C3	**0.82**	-0.12	0.01	0.03
C4	0.21	0.10	**0.62**	0.07
C5	**0.69**	0.08	-0.21	0.18
C6	-0.04	**0.82**	-0.06	-0.05
C7	0.06	0.10	0.02	**-0.73**
C8	0.17	0.39	**0.23**	0.35
C9	0.06	**0.81**	-0.01	-0.10
C10	-0.11	-0.24	0.57	**0.02**
C11	**0.82**	0.21	-0.02	-0.13
C12	-0.01	0.32	**0.64**	-0.05
C13	0.09	**0.74**	0.06	0.03
	Controllable by Self	**Controllable by other**	**Stability**	**Locus**

	Factor 1	Factor 2	Factor 3	Factor 4
Factor 1	1.00			
Factor 2	.33	1.00		
Factor 3	-0.08	0.14	1.00	
Factor 4	-0.26	0.07	-0.15	1.00

Factor analysis performed on the Profile of Mood State data revealed discrepancies between the sample data and the data normed on psychiatric outpatients and college students (McNair et al., 1971). Those differences were analyzed and the general factor representing anxiety and tension was chosen to represent the negative stress emotions for the purpose of testing the theoretical model.

The proposed model (see Figure 1), including all relevant relationships, was tested using Bentler's (1995) program for the analysis of structural equations (EQS). A latent variable approach was used to represent the role of attributional cognitions and stress emotions. Due to the small sample size (n=60), model testing was limited to 8 variables (Bentler, 1995). Control-by-self was chosen as the cognitive-attributional construct for model testing. The decision to use Control-by-self was based on previous research on health outcomes and stress which utilized this cognitive variable (Borysenko, 1984; Peterson, 1981; Levy, 1987; Morley and Herbert, 1991). The latent variable representing cognitions was produced using the first two variables in factor 1 (see table 1) which measured the subject's perception of personal control over the stressful event. The third control variable (C11:over which you have power) was excluded because 9 of the subjects sought clarification from the experimentor. Consequently 25% of the subjects either did not answer the question or picked a median score of (3). The other measure of control (Factor 2, control-by-other) was not used because sample size did not permit additional variables in the statistical model. Further, the factors representing both control-related attributional constructs (factor 1 and

factor 2) correlated (see Table 1). Models including additional emotional factors were also limited by sample size. The stress-emotion factor (anxiety) was represented by four questions from the original instrument. The adjectives included in the anxiety scale were: b1=Tense, b6=Shakey, b12=Uneasy and b16=Nervous. Each of these adjectives was used in a latent variable representing a stress-emotion. Two separate immune measurements were used to verify the model; Lytic units (functional analysis of natural killer cells) and Phagocytic test of monocytes (a functional assay used to measure the ability of monocytes to phagocytize a bacterial challenger). Correlations of all variables used in the model are shown in Table 2.

Table 2: Correlation Matrix of Variables Used in the Statistical Model.

	B1	B6	B12	B16	C3	C5	LYTUNIT	PHAGO-CYTOSIS MONOCY
B1	1.0							
B6	0.52	1.0						
B12	0.57	0.45	1.0					
B16	0.70	0.55	0.62	1.0				
C3	0.10	0.07	0.05	0.03	1.0			
C5	0.07	0.20	0.08	0.08	0.68	1.0		
LYTUNIT	0.10	0.07	0.18	0.10	-0.11	0.00	1.0	
PHAGO-CYTOSIS MONOCY	0.09	0.17	0.20	0.09	0.16	0.12	0.24	1.0
CRONBACH ALPHA = 0.69								

Assay data for Natural Killer cell (Lytic Units) and Phagocytosis were gathered and the anchor group was compared to three stress-groups separated by length of time exposed to the stressor. Further, an aggregate anxiety score and an aggregate controllability score were also used as comparison measures across stress-groups. Results are displayed in Table 3.

Table 3: Mean Scores and Variances of a Composite Measurement of Cognitions, Emotions and Immune Response Relative to Time Exposed to Stressor. An Anchor Group and Normal-Assay-Sample are Included.

Measure	Anchor Group	(N=14)	1-30 days	(N=9)	30-180 days	(N=14)	180+ Days	(N=19)	Normal Assay
	Mean	Variance	Mean	Variance	Mean	Variance	Mean	Variance	Normal Range
Lytic Units	**3.57**	12.26	**5.22**	40.69	**3.07**	5.30	**4.53**	12.71	**1-3**
Resp. Burst Monocytes	**40.06**	76.92	**40.50**	68.45	**36.32**	54.24	**42.60**	122.12	*
Phagocytosis Monocytes	**1,059.11**	58,711.50	**1,112.49**	33,684.85	**1,053.70**	15,331.74	**1,021.40**	117,908.15	*
Cognition	**5.50**	6.58	**4.38**	5.41	**5.23**	6.19	**6.00**	6.89	*
Emotion	**7.29**	8.99	**12.67**	11.25	**11.71**	14.84	**10.95**	14.50	*

In order to account for normal theory assumptions, kurtosis and skewness were measured across all relevant variables. All of the variables with the exception of Lytic Units and Phagocytosis-by-monocytes were within +/- 2 range, suggesting that the sample size is appropriate for the use of EQS (Bentler, 1995).

The results of the proposed models are shown in Figure 2a and 2b. On the basis of the maximum likelihood method used in the EQS program, the model fit the data quite well, Biological=Lytic unit: $X^2(12)=8.62$, p=.74, NFI=0.94(CFI=1.0). Biological=Phagocitic assay: $X^2(12)=6.41$, p=0.89, NFI=0.95 (CFI=1.0).

To further examine the role of cognitions and emotions in the immune response, two additional models were tested. The model tested was identical to the one presented in Figure 2a except that the relationship between cognitions and emotions was reversed and the arrow from emotions to immune measures was directed from the cognitions to the immune response; in effect a reversal of the relationship. Results show that the fit of this model is not adequate, X^2 (11)=30.83, p=.0011, NFI=0.86 (CFI=.90). The model was shown to be a poor fit by the significant chi-square statistic which suggest that there is significant variance not accounted for by the model.

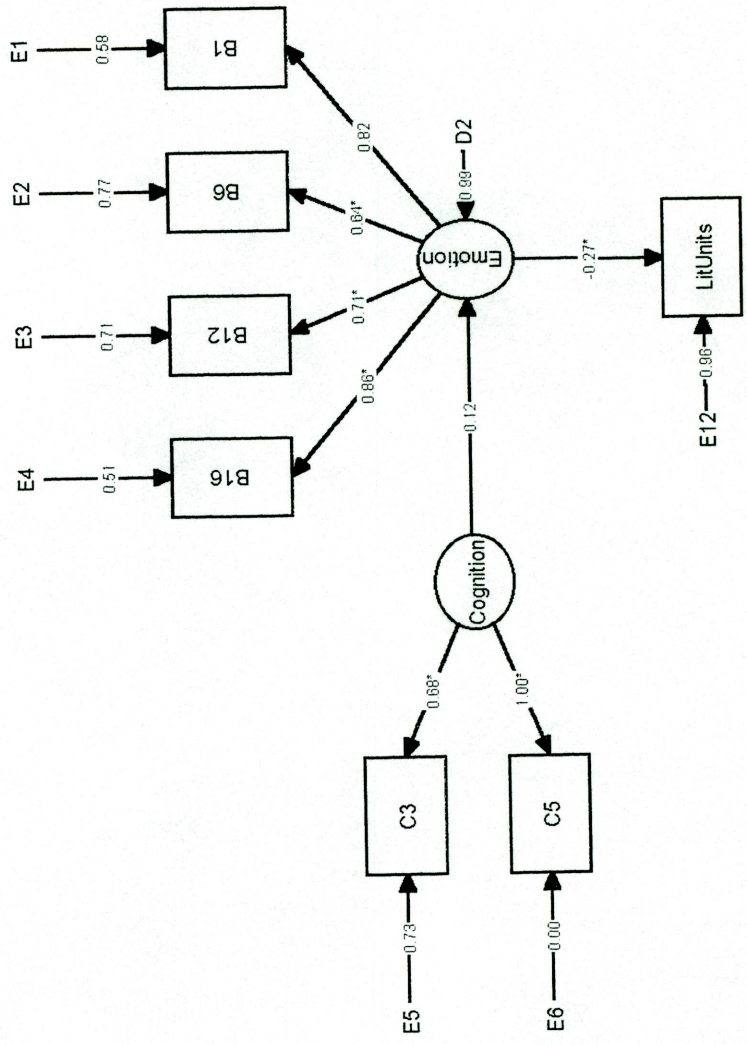


Figure 2a: Statistical Model with Lytic Units as Immune Measure

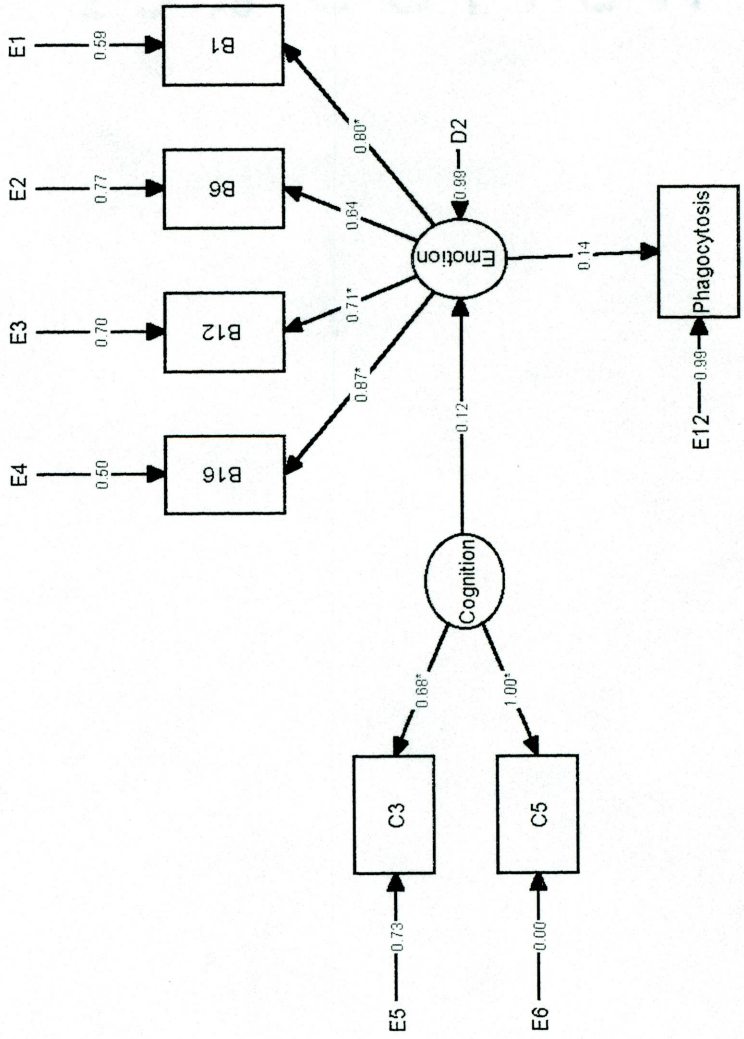


Figure 2b: Statistical Model with Pagocytosis by Challenged Monocytes as Immune Measure

The second model was set up much like the Cannon-Bard theory of emotion and cognition. According to this textbook theory, cognitions and emotions jointly and simultaneously impact physiological response. The model in Figure 2a was changed so the connections from both factors were directed at the immune measure. EQS showed that this model did not fit the data at all: X^2 (7)=242.5, p=.001, NFI=-.099 (CFI=0.0) A final model was posed in which emotions accounted for cognitions and both cognitions and emotions accounted for immune response. EQS demonstrated again that this model does not fit the current data: X^2 (10)=30.93, p=.001, NFI=0.86 (CFI=.90). Chi-square tests revealed in all cases that significant variance was unaccounted for.

Discussion

The results from this study strongly support the proposed theoretical model (see Figures 1, 2a, 2b). The effects of cognitive processes on emotions and the corresponding impact of emotions on the immune system is reinforced and a directional link is established. This is particularly interesting in light of current interest in mind-body interfacing. Previous research in disciplines such as health psychology, behavioral medicine and psychoneuroimmunology have all noted these relationships and speculated at the directionality of the cause-effect relationship.

Although the results show only mild emotional variance accounted for by cognitions (0.12), the results are consistent across immunologic measures. This is to say that the relationship was stable and the only real change in indices occurred at the point of immunologic effect. The fact

that the stress emotions had a negative relationship with natural killer cells is consistent with the literature and was predicted. The immunologic assay accounting for phagocytosis by monocytes was positively influenced by anxiety. This is not intuitive but does make sense in light of previous research on the dynamic and compensatory nature of the immune system (Landman et. al., 1984; Glaser 1990). The immune system is in dynamic-fluctuation seeking a homeostatic position of optimum efficiency. When one sub-system is compromised another branch of the system may increase its functioning to compensate until the compromised sub-system restabilizes. This might explain the positive relationship between anxiety and phagocytosis and might be seen as a system adjustment accounting for negative changes in natural killer cell functioning.

From an attributional perspective it is interesting to note that only one latent variable, comprised of two items, accounted for as much (0.12) of the variance in emotions. This suggests that their are other attributions or cognitive mediating variables that, if tapped, may account for even more of emotion. Previous attributional models (Weiner, 1985, Betancourt, 1992) have shown strong directional links between attributions and emotions. The data from this study cross validates those findings and suggests a new direction for this line of investigation; a direction that includes biological consequences for these cognitive processes.

The positive relationship between control and anxiety is also predicted. If parents see "the cause of" there child's illness or injury

something within their control then they would feel guilt and the consequential anxiety associated with that guilt. This apparently small relationship (0.12) should also be understood in light of the many types of cognitive attributional processes yet to be explored. With an increase in the sample size, additional attributions can be added to the model. The validation of the proposed theoretical model suggest that additional cognitive variables may account for more of the variance in emotions

Stress researchers have provided considerable amount of data on the relationship between stress and immune functions. Experimental designs with humans have been limited to acute laboratory stress studies, while animal studies have been limited by the deficiency in higher level cognitive functions. This has left a void between what is theorized using the animal model and what is explored with human subjects. Although stress emotions such as anxiety have been negatively related to immune functions (Cohen, 1994; Keicolt-Glaser et al., 1987) the ability to study causality in humans is limited.

These design considerations point to the potential contribution of causal modeling techniques. To employ causal modeling technique requires a firm understanding of research, theory and practice and the ability to propose a model before gathering the data. Because current ethical and legal issues prevent experimenters from exposing subjects to chronic and intense negative stressors in order to measure immune response, causal modeling remains a plausible alternative. This does not rule out experimental designs, but it does limit the field of potential research protocols.

The results from this study do not originate a new model, instead they simply join two current yet separate models; an attribution-emotion model proposed by attribution theory and a stress-immune model proposed by psychoneuroimmunology. This hybrid theoretical model is simplistic and is not intended to answer questions more suitable for experimental designs. In fact we believe this research presents more questions than it answers. The results however, are quite exciting and include relevance to such diverse fields as: immunology, psychology, cognitive science, medicine, and biology.

The proposed theoretical model was tested in subjects whose emotional states were attribution-dependent (see Figure 1), having had at least 48 hours to process a stressful life event(s). Implications for a model which can explain and operationalize the role of the cognitive components in the immune response may have critical influence on current medical practice as well as preventative medicine, recovery medicine, psychotherapy, and bereavement work. These implications may manifest themselves in the form of: a more holistic approach to medical treatment, education of those at risk for opportunistic infections, better psychological treatment for those with life threatening diseases such as cancer and HIV infection, a better understanding of mind-body continuity, and a general enhancement of the quality of life.

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