Psychoneuroimmunology:  
An Interpretation of Experimental and Case Study Evidence Towards a Paradigm for Predictable Results 

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This paper surveys a number of key experiments and case studies relating to psychoneuroimmunology. It finds that most techniques to influence or even direct the immune system via the mind fall into a series of theoretical categories called passive, active and targeted effects. By examining the results of experiments and studies in the light of these categories a number of important conclusions are drawn. These conclusions explain differences in experimental results, describe those variables that appear to be central to obtaining results, and describe in detail where experimentation should be concentrated to further knowledge of psychoneuroimmunology.

Psychoneuroimmunology does not have a precise object that is the focus of investigation. Rather, it is about a series of relationships between mind, nervous system, and immune system. The nature of these relationships and the ensuing discussion can, in turn, cover the spectrum from the abstract to the concrete, from philosophical distinctions with their origins in Descartes, to the physics and chemistry of molecular biology. However, unlike many philosophical conundrums which may only be decided through lengthy and skilled analysis or through thought experiments, these relationships indisputably have empirical consequences.

Many discussions of psychoneuroimmunology in the medical literature are strictly empirical, which is no doubt beneficial since empirical experiments define the factual boundaries within which the various relationships between mind, nervous system and immune system exist. However clearly these boundaries are delineated, the relationships themselves, of one subject to another, are by no means clear. Although a certain body of facts has been determined, the implications for these relationships has not been worked out. This article, as opposed to other review articles, rather than focusing strictly upon the facts that have been established in psychoneuroimmunological experiments, and what these facts may mean for the establishment of other facts, will be concerned with the facts and a therapeutic framework they seem to imply for the relationships with respect to the entities involved.

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I submit that I will not satisfy the extremes: that is, those who view these relationships in a highly theoretical or even spiritual manner will not be happy with my speculations because I do not go beyond what is empirically implied; but those empirically inclined will be equally frustrated since I will not elaborate the physical mechanisms by which these interactions take place. The goal will be to account for differences in experimental results, and describe how consistent results might be obtained in experimental and clinical situations.

For the purposes of our discussions, the terms mind, nervous system, and immune system are defined as follows: mind refers to thoughts and feelings experienced consciously, subconsciously, and unconsciously; nervous system refers to the autonomic nervous system. By analogy with computers, the mind constitutes software, the nervous system constitutes hardware. The immune system is comprised of bone marrow (such as stem cells), skin and other cells and mechanisms involved with fighting infection and disease.

Through a series of abstract questions, and relating the empirical facts to them, a theory can be constructed to account for experimental differences and suggest directions for further experimentation:

What happens to the immune system when the mind is not attending to it, consciously or unconsciously?

What happens to the immune system when the mind is not trying to communicate with it or otherwise affect it? Is the immune system affected anyway? What sort of effects can be observed?

Is the nervous system acting upon the immune system without our mind doing anything?

What happens when the mind is attending to the immune system?

Can the mind communicate with the immune system in order to change something that the immune system is doing?

What does the mind have to do, via the nervous system, to change the immune system?

Is there some specific type of thinking or feeling that indicates the immune system will be affected?

Can the mind use the immune system as an instrument? That is, can it communicate with the immune system and direct it to some action with the mind or nervous system cannot themselves affect?

Can effects be measured?

Are effects efficacious?

For the purposes of distinction, I will label three categories into which these questions roughly fall. The first category is called passive effects; the second, active effects; and the third, targeted effects. These three categories form the logical possibilities for the exploration of the mind/body relationship with respect to the immune system. Passive effects are the mind as it affects the immune system without any specific intent to do so. Active effects are the mind as it affects the immune system with the intent of affecting it. Targeted effects are the mind as it affects some disease, symptom, or immune reaction via the immune system. The converse case, does the immune system affect the mind, or are there mechanisms for feedback where the intended effect originates from the immune system, is a curious question which will be addressed later on.
Passive Effects

There are a fair number of experiments demonstrating that the mind or mental or emotional state of an individual has a bearing on the immune system though the immune system is not the intended beneficiary of such mental processes. Since the mind interprets perceptions and therefore mediates the body’s response to them, it is expected that the immune system would respond. For example, the immune system appears to have a specific role in the fight/flight response in that it reacts to prepare the body to better fight infection (O’Leary, 1990). It appears that the immune system can be affected by the mind positively or negatively. Some examples of this phenomena include: that although the immune system is not the object or subject of depression, it is affected negatively by depression; that during depression the immune system does not function up to normal expected rates putting a person at risk for disease (Zachariae et al., 1991); the immune system is negatively affected by a negative self-evaluation (Strauman, Lemieux & Coe, 1993).

What is discouraging in terms of experimentation is the complexity and specificity of the variables involved. There are so many different effects on the immune system caused by various mental states that it seems a different immunological effect exists for every specified mental state. There are two clear implications however: 1) the immune system is a more or less homeostatic system (Ader, Cohen & Felten, 1995); and 2) the relationship of the brain to the immune system is bidirectional, meaning that information in the form of various peptides passes back and forth between the two systems (O’Leary, 1990; Gruber et al., 1993). Additionally, clear physiological structures connecting the nervous system and the immune system are well established (Farrer, Kilian, Hill, Ruff & Pert, 1987).

Certain mental states appear to have a direct and measurable overall positive effect on the immune system including: relaxation, classical conditioning (Pavlovian), hypnosis, exercise, and self-disclosure under certain circumstances (Kiecolt-Glaser & Glaser, 1992). Guided imagery and biofeedback affect the immune system (Gruber et al., 1993). One important and suggestive study concerned the use of group psychotherapy and hypnosis with women with metastatic breast cancer. This study showed positive results on the mortality rates of the subjects (Spiegel, Bloom, Kraemer & Gottheil, 1989). Hypnosis has been shown to significantly increase longevity in cancer patients, though it was not used to attack neoplasms in this study (Newton, 1982). Another effect is suggested in a study of men who underwent group therapy. What is interesting about this latter study is that while there were some immediate effects on the cell counts of the immune system, some further effects on the cell counts didn’t show up for six months, such as an increase in T-cells (Fawzy et al., 1990). Changes over a sustained period of fifteen months were also seen in a study examining relaxation, guided imagery and biofeedback (Gruber et al., 1993). The immune system appears to be passively affected by both positive and negative life events over time.

It is counterintuitive, but informative, to ask the following questions: Could the immune system send a signal to the nervous system to tell the mind to get it out of its depression? Could the immune system change neuro-chemistry to change a person’s thinking to relieve the stress that is causing the immune system to function at a lower level? Does the immune system create any neurohormones to communicate back to the nervous system? Why shouldn’t people feel happy because the immune system needs to improve its functioning and tells the nervous system to feel happy? There is an animal experiment on this feedback loop, but, unlike hunger, it does not appear that the body has any way of telling the mind or nervous system that the immune system is in need of specific nourishment. In the experiment, mice appear to behave in ways suggesting awareness of their immunological dysregulation. (Ader et al., 1995; Ader, Grotta, Moynihan & Cohen, 1991). It also appears that interleukin-
2 may regulate mood, affect, and cognitive states (Rossi, 1996; Glaser et al., 1990). Although the relationship may be bidirectional, it is not clear or thoroughly examined.

The immune system doesn’t get hungry (to extend the metaphor). One wonders if more conscious control of the immune system might be obtained thorough some sort of electronic monitoring or biofeedback. The variety of results from so many experiments in which the immune response varied according to the mental state of the subjects suggests the possibility that the nervous system sets the homeostatic limits of the immune system based upon our most consistent mental state. Mental life is highly dynamic, and it appears that consistent impact on the immune system occurs when there is some specific variable that stays constant over time -such as chronic stress, or long-term relaxation. But what does this imply in terms of the experiments discussed? It suggests that when a stressed individual’s environment is restored to a normal or positive level of functioning, homeostasis is restored to the individual, and this is reflected in the immune system. Consequently, when studies are done on non-stressed subjects to measure changes in the immune system with relaxation or other passive means, the results are negative (Kiecolt-Glaser et al., 1992). Perhaps, the immune system is at its correct levels when there is no stress. This suggests that normal ranges of immunological cells may already be at their upper limits and there is really no place for them to go but downwards. Hence, one would expect that long-term chronic stressors would tend to degrade the performance of the immune system for two reasons: 1) bodily and psychological resources are not unlimited, and 2) the immune system may be regulated by our most consistent or perhaps dominant psychological state. Although it is clear that long-term chronic stressors do degrade immune system performance (Kiecolt-Glaser et al., 1992), the exact reasons or mechanisms are unknown.

Consider the possibility that in healthy individuals the immune system is already where it is supposed to be in terms of levels of various cells. Are the settings of these various limits, such as the percentage of NK cells, or T-cells, a response to some early immunological event? Are these limits set genetically? Are other factors involved? It would be very interesting to attempt an immunological history of an individual(s), and see for example, if their immune systems had compensated for frequent early infections. It would be significant to study the history of an individual and how his/her system was affected by important life events as they occurred and within the aftermath of the event. For example, do certain environmental factors such as the consistent comforting of an infant change the settings of the immune system? These are important questions which have not been explored. Longitudinal studies in psychoneuroimmunology could prove to be extraordinarily fruitful.

**Active Effects**

The concept of active effects refers to the question of what happens to the immune system when thought or feeling is directed at changing or affecting it. Although there are far fewer studies done on what might be termed active effects, they do exist and draw some important conclusions. Making the immune system the subject of imagery and direct suggestion can affect immune function in a positive direction (Zachariae et al., 1991; Hall, Mumma, Longo & Dixon, 1992; Gruber et al., 1993). Trance induction with suggestions to increase certain immune functions has also been found to positively affect the immune system in highly hypnotizable patients (Ruzyla-Smith, Barabasz, Barabasz & Warner, 1995).

It is important to note a particularly well-executed experiment which had a negative result. Highly hypnotizable subjects in this study could not enhance or suppress an immune reaction to an antigen (Locke et al., 1994). One of the unfortunate conclusions drawn by the authors is:
At the same time, the study may possibly reflect reality, and the popular belief that individuals in general can use their minds to control their immune system may be more of a wish-fulfilling fantasy than a real, psychobiological phenomenon.

Such a conclusion would only be warranted if the exact mechanism by which hypnosis affects the body was known. Since it is not, the fact that in a particular instance hypnosis did not produce the desired effect does not logically lead to the conclusion that all such effects are “fantasy.” But this does provide some important information that leads in more positive directions. Since other well-controlled experiments have positive results using active effects, the question that arises is, what is the difference? One critical difference is one of direction. Instead of trying to tell the immune system how to react to a specific antigen, other studies suggested that the immune system can function more properly if certain sorts of goals are reached, such as having more killer cells. It may be that through the use of hypnosis, or guided imagery or bio-feedback, the immune system can be influenced, but not necessarily controlled.

In retrospect, it is easy to see that it is important to distinguish experimentally between active and passive effects. When imagery is combined with relaxation, it is difficult to determine which variable, or combination, caused the immunological change. Since relaxation or other stress-reducing activities seem only to have an effect on stressed subjects, invalid conclusions suggesting that relaxation is not effective may be drawn when active effects and relaxation are used together.

What is remarkable about the phenomena of active effects is that, through images and words, the body is asked by the mind to produce a certain type of cell and then appears to produce it (Ruzyla-Smith et al., 1995). Through the course of the experimental protocol, the subjects’ bodies produced exactly the cells they were asked to produce. This suggests that not only is the immune system connected with the nervous system, but the nervous system can communicate a specific request of the immune system and the immune system “hears” and accomplishes the request. It is one thing to lower blood pressure or heartbeat rate, which are more or less gross physiological functions; it is quite another to produce a specific cell simply by virtue of trance state and visualizing the cell. This suggests that the nervous system can exert a microscopic influence over parts of the body to which it is connected. Another example of this influence is a study in which hypnosis was used to regulate immunoglobulins in the saliva of children (Olness, Culbert & Uden, 1989).

Examining further Locke’s negative outcome, it should be noted that Locke et al. (1994) were not measuring changes in the immunological system, such as T-cells, but were measuring a particular immunological reaction. Their results suggest that immunological reactions cannot be controlled, but it does not follow that immunological changes, such as cell counts, cannot be affected. These are separate and independent variables. While it may not be possible to control, hypnotically or otherwise, a specific physiological reaction, it may be possible to influence, at a cellular level, the physiological conditions under which the reaction takes place. That is, it may be possible to affect immunological changes, such as cell counts, which in turn may change the way the body reacts to a particular antigen. Unlike gross physiological phenomena such as heartbeat, the “micro-environment” (Ader et al., 1995) of the relationship between immune system and nervous system does not lend itself to a strict causal chain.

Another issue is the correlation of hypnotizability with immune system changes. Since standard measures for inducing trance were most used in experiments, it is not clear whether,
if greater care or more extensive training were employed, immune changes could be produced in persons less hypnotizable. Unfortunately, the one experiment where a number of statistically significant positive changes in the subjects’ immune systems occurred without hypnosis, hypnotizability was not included in the list of variables (Gruber et al., 1993). Thus, it is not clear if hypnotizability contributed at all to that outcome.

There is clinical evidence that other factors significantly influence hypnotizability. The fact that standard hypnotizability measures use a direct authoritative approach has specific consequences. It means that studies which employ such measures do not reflect the possible outcomes which might have been obtained through the use of indirect suggestion. With some individuals, indirect suggestion may be more effective in trance induction (Erickson, Rossi & Rossi, 1976). It appears that new studies must be conducted with different means and measures to obtain more accurate results. The effectiveness of hypnosis in eliciting physiological responses may also be underreported. Clinically, even “unhypnotizable” patients (as measured by standard instruments) can be hypnotized with measurable results (Barber, 1980).

**Targeted Effects**

Can the immune system become an instrument of the mind and nervous system such that the immunological system is enlisted to change a specific symptom or disease condition or is directed not to respond to a specific antigen? This is the question of targeted effects. Few truly controlled studies of targeted effects exist, though there are several controlled studies using hypnosis to control an immunological skin reaction, such as allergic response and the removal of warts. Universally, such effects are elicited through hypnosis and hypnotic suggestions. There do not appear to be any studies in which targeted effects are brought about through some other means such as biofeedback. A very clear and well-controlled example of the use of the mind to target a specific problem is in the removal of warts. Warts can be made to disappear through hypnotic suggestion (Spanos, Stenstrom & Johnston, 1988; Ewin, 1992), though the success rate is far higher with children than adults (Ewin, 1992). A well controlled study also exists for severe intractable irritable bowel syndrome (Whorwell, Prior & Colgan, 1987).

Both skin inflammation and allergic response have not responded to hypnotic suggestion in high hypnotizables in some studies (Beahrs, Harris & Hilgard, 1970; Locke et al., 1987; Locke et al., 1994). The question of why hypnosis is successful in some situations (wart removal in children) and not as successful in others (wart removal in adults) or not successful at all (as in skin inflammation studies) is very important for determining how the immune system can be utilized as an instrument.

The measurement of effects on the immune system is problematic at best. The immune system is highly individualized in terms of the individual’s disease history, and in terms of variables such as metabolism, personality, genetic factors and sleep. It has been suggested that by closely timing the collection of data in blood samples, better measurement might be possible (Kiecolt-Glaser et al., 1992). However, this is questionable since some effects on the immunological system may not show up for months (Fawzy et al., 1990). This is supported also by morbidity rate (Spiegel et al., 1989) and cell counts (Fawzy et al., 1990). It seems unlikely that well-timed measurement of immunological functions can be used to validate experiments since individual differences and the number of variables simply overwhelm the analytical tools available. The immune system appears to be an interactive system (Kropiunigg, 1993), so perhaps instead of looking to measure particular chemicals and their effect on outcome, it would be more sensible to look for positive outcome with respect...
to the disease or symptom and then look to see what factors arose over time when that outcome occurs. Sometimes positive changes to the immune system through psychotherapy did not show up for six months or more (Gruber, Hall, Hersh & Dubois, 1988). Until a set protocol is established which predictably shows effects for a majority of participants, attempts to actually measure immune system changes will be impeded by the immune system’s reactivity and volatility. Hopefully, some important plateau within an individual’s immunological level of functioning may be recognized. Then comparisons across individuals may reveal commonalities.

While much of the research on targeted effects shows promise, little is predictably efficacious. There are two themes to consider with respect to efficacy: 1) the interdependence of the three categories of psychoneuroimmunological effects; and 2) the problem of enlisting the unconscious mind.

Let us try, from a theoretical point of view, to account for some experimental differences with respect to psychoneuroimmunological effects. In one experiment, relaxation was not found to have a significant impact on raising the level of function in the immune system (Ruzyla-Smith et al., 1995), whereas in some experiments with distressed subjects it did have an impact (Kiecolt-Glaser et al., 1992). This suggests that if one uses a technique that is attempting to passively affect the function of the immune system on subjects who are well-adjusted and happy, one would not expect to find any statistically significant differences. However, if one were to attempt to actively induce an immunological response, such as an increase in B-cells, in a stressed individual without also including relaxation, one would expect, according to the paradigm introduced, to fail. It may be that active effects are dependent upon the base functioning of the immune system. If that functioning is not addressed through relaxation or some stress-reducing strategy, it would seem that active effects would not appear. Furthermore, if the base level of an individual is already normal, one would not expect relaxation or other techniques used to passively affect immune function to succeed since optimal functioning already existed.

Similarly, one could not expect to be successful in targeting a particular symptom or disease condition if the immune system was itself compromised either through stressors, disease, or chemotherapy. Though it may be the case that it is not necessary to induce an active effect to communicate to the immune system that it needs to fight off a disease, nevertheless, it would appear from a practical point of view, that if you can communicate to the body what it needs to do to accomplish the goal of fighting off a disease, this should be helpful. To return to a point made earlier regarding the negative outcome of Locke and coworkers (1994), there were no hypnotic suggestions regarding how the immune system ought to go about either suppressing or enhancing the immunological reaction to the antigen in their study, such as creating certain cells or suppressing others. Since it appears the immune system may not be controlled through hypnosis in the way body temperature may be controlled, it may be necessary to suggest certain means such as the growth of certain cells which would handle the antigen.

From a theoretical perspective, the three categories of relationships between mind and immune system as represented by the concepts of passive effects, active effects and targeted effects, may demonstrate a kind of continuum of immune functioning. Passive effects must be taken into account for the general well-being of the immune system, active effects for generating the necessary weapons against disease, and targeted effects for directing the weapons against a specific target.
The second problem of efficacy is the enlistment of the unconscious mind. In various studies, active effects have been seen only in highly hypnotizable subjects (Ruzyla-Smith, et al. 1995) and the targeting of warts through hypnosis was more successful in children (Ewin, 1992). Children have been shown to be particularly hypnotizable, and this has clinical implications (Bowers & LeBaron, 1986). In analyzing the problem of eliciting physiological responses, there appear to be two central variables. First, it should be recognized that physiological responses in hypnosis are learned skills. There is some suggestion, but no experimental confirmation, that by learning to control progressively difficult physiological responses, subjects gain confidence in the process of hypnosis and are therefore more capable of such responses (Golan, 1986). The assumption made in most of the experiments is that because someone is highly hypnotizable, they therefore are more likely to be able to control physiological responses. This seems a valid assumption but it warrants further examination. While a child gifted in mathematics but without training would probably fail to solve a differential equation, young adults of average mathematical ability can be taught to solve such equations. It may be that learning to elicit certain types of physiological responses requires a great deal of hypnotic skill and that while some persons are potentially gifted in using that skill, they may require a fair amount of training. Incentives or behavioral rewards for learning the skill may increase the speed at which it is grasped. It is documented that when people have a great deal of pain they can learn advanced hypnotic techniques even if they are not particularly hypnotizable or even if they are unhypnotizable (Barber, 1980).

To establish a valid premise for future hypnotic/physiological experiments, an experiment needs to be done to resolve the issue of the effect of hypnotizability upon outcome. A simple series of increasing difficult hypnotic tasks which elicit a specific physiological state could be devised. Then a comparison in outcomes could be made between two groups. One group (the control) would be untrained, the other would be trained. A particular task to prove that the trained group had learned hypnosis would have to be chosen, and the depth of the hypnotic state would also have to be measured (as it might turn out to be an important variable). Each of the two groups would, in turn, be composed of a distribution of persons chosen by their hypnotizability ranging from not hypnotizable to very hypnotizable. Such an experiment would provide a sound basis for future work by establishing hypnotizability as critical, or showing that some other variable is critical.

It would seem reasonable that training which aims to produce progressively more difficult physiological responses would make physiological responses more likely in general, as well as produce a stronger faith in the use of hypnosis to affect change.

Another aspect of the nature of belief which enters into the clinical and experimental situation is this: a person’s view of what is possible in the world, which might be termed his/her event horizon. This horizon needs to be expanded in order to make use of hypnosis. Children and adults who are highly hypnotizable are natural candidates for the use of hypnosis. (It would be interesting to measure if the level of magical thinking in adults correlated with success in eliciting immunological responses rather than hypnotizability.) Nevertheless, one does not consciously communicate with the immune system in the same way one can consciously lift an arm. The vehicle which appears to facilitate all communication through the nervous system and with the immune system is the unconscious. But the unconscious can easily sabotage our efforts to initiate change through various means, such as resistance or interference, even if a person is hypnotized (Kalt, 1986). Therefore, even if a positive suggestion is made for a physiological response, the therapist needs to verify that the unconscious mind has in fact accepted the suggestion. There appear to be two avenues by which the likelihood that suggestions will be accepted and acted upon is
increased. First, depth of trance appears to be a variable in post-hypnotic suggestions (Berrigan, Kurtz, Stabile & Strube, 1991). Second, one can take a “shot gun” approach; that is, try various suggestions until one has been accepted and verified through an unconscious ideomotor response to questions regarding whether the suggestion is accepted by the subject (Madrid & Barnes, 1991).

In one study where physiological responses were consistently elicited (Madrid et al., 1991), these basic criteria were met: 1) the over-all well-being of the patient was taken into consideration and acted upon (passive effects); 2) the mechanism/chemicals for affecting the disease condition were communicated as precisely as possible during a trance state (active effects); 3) the disease condition was targeted as precisely as possible (targeted effects); and 4) the unconscious mind was enlisted and it was verified through ideomotor response that the suggestions had been verified.

It is the very last item which appears to be the most critical. In most studies, confirmation that the body will be changed is only verified after the change has been effected by looking at blood studies. But there are really two sides to the interaction of mind and body. In looking only at the body for change the mind is left out. Yet, the mind cannot be the only place to verify for change since the mind does not appear to normally sense feedback from the immune system (vis-à-vis hunger). However, asking the unconscious mind if it will communicate the information it has given to the body would seem to be the most reliable way of determining whether a particular intervention would have a good probability of being effective. Still, such results might be limited; that is, the unconscious mind may not agree to total results. This is another argument for a lengthy training period in which progressively more profound physiological effects are produced. On the other hand, patients who did not particularly ascribe to the benefits of relaxation and guided imagery obtained immunological benefits anyway (Gruber et al., 1993).

Protocol Development

It appears that the next step in the development of successful techniques in the use of the knowledge base of psychoneuroimmunology is to design a protocol for a specific disease entity with the goal of overcoming the disease or making a significant difference in outcome. It has already been suggested that relaxation and guided imagery be used to augment traditional cancer protocols (Gruber et al., 1993). Though procedures have been developed using ideodynamic principles (Rossi & Cheek, 1988), no protocol has yet to take into account the particular requirements of passive, active and targeted effects.

Rather than viewing such interventions as a means of making patients more comfortable, they should be viewed as having the capability to make the difference in disease outcome in, at minimum, some individuals. Such a protocol would acknowledge the various peaks and valleys of treatment and gear individual psychosocial and family interventions towards alleviating anticipated stressors. Such a protocol would work at creating sufficient hypnotic skill, skill in relaxation, and skill in guided imagery, which appear to be required to effect physiological changes. Control groups would be separated out for control of passive, active and targeted effects. While such interventions may not be successful in every case, it seems likely, given the experimental evidence, that such interventions would make a statistically significant difference in disease outcome and morbidity.

References


