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A Review of the Impact of Hypnosis, Relaxation, Guided Imagery and Individual Differences on Aspects of Immunity and Health

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This review considers psychological interventions involving relaxation and guided imagery targeting immune functions. The review provides evidence of immune control accompanied by reports of enhanced mood and well-being. Three recent investigations of the author and his colleagues with self-hypnosis training incorporating imagery of the immune system are outlined. In two studies, hypnosis buffered the effects of stress on immune functions in medical students at exam time, and the comparison of self-hypnosis with and without immune imagery confirmed advantages to targeted imagery for both immune function and mood, and importantly, fewer winter viral infections. The implications for health were investigated in a third study in patients with virulent and chronic herpes simplex virus-2 HSV-2). Six weeks of training almost halved recurrence, improved mood and reduced levels of clinical depression and anxiety. Immune functions were up-regulated, notably functional natural killer cell activity to HSV-1. Individual differences in hypnotic susceptibility and absorption have typically been found to predict efficacy. New replicable evidence is reviewed of the importance of cognitive activation, a personality difference whose neurophysiological underpinning is consistent with left hemispheric preferential influences over the immune system. Now that the validation of psychological interventions includes advantages for health, this field of enquiry, which has been characterised by modest, small scale, largely preliminary studies, warrants a greater investment in research.

Keywords: Hypnosis; Imagery; Immunity; Laterality; Personality; Relaxation

INTRODUCTION

Convincing evidence is steadily accumulating of how the psychology of the individual has profound effects on many facets of health including susceptibility to illness and outcome, well-being and ageing. The field of Psycho-neuro-immunology (PNI) is contributing to this foundation of knowledge following the delineation of pathways allowing mutual influences between the brain and the immune system (Ader *et al.*, 1991; Leonard and Miller, 1995; Evans *et al.*, 2000). There have been demonstrations too numerous to mention of immune compromise in association with disease and stress which have been reviewed elsewhere (O'Leary, 1990; Ader *et al.*, 1991; Bennett Herbert and Cohen, 1993; Leonard and Miller, 1995; Evans *et al.*, 2000). At the same time, psychologically directed therapies have been shown to reduce stress and enhance well-being for over half a century, evidence which has included patients with compromised immunity. However, what has tended to be lacking are studies, which in addition to evidence of improved well-being, have provided evidence of strengthened immune competence, and ideally, the critical further step of evidence of improvements in health. Nevertheless, the evidential base is growing step by step and has occasioned this review.

The validating steps of immune parameters and health are necessary because of the complexity of immune functions and the complexity of stress. Both complexities are poorly understood, such that changes in the direction of up-regulation or down-regulation are ambiguous vis-à-vis putative immune strengthening. Accordingly, objective and self report measures of stress status and health are mandatory to help with validity. Even so, as this review will show, these principles alone are unable to reconcile the complexity of a highly redundant, dynamic system full of checks and balances, redistribution and migration. In the absence of models allowing predictions to be made

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which encompass the functional complexity at this still early, data gathering stage of investigation, the hypothesised outcomes of psychological interventions on immune parameters have been unitary and unidirectional, i.e. predicting up-regulation of the single or multiple measures of immunity assayed. These typically have included numerative measures of white blood cells including lymphocyte and neutrophil subsets and natural killer cells (NKC), functional assessment of NKC and of lymphocyte competence through blastogenesis to mitogens, cortisol from saliva or plasma, a widely used measure of humoral immunity indexing stimulation of the hypothalamic-pituitary adrenal system, and immunoglobulins as an indicator of mucosal immune regulation measured in saliva or serum.

It has been necessary to limit the scope of the review by focussing on those relatively neglected intervention studies which have included an immune parameter. This has meant excluding intervention studies centered on the well-being of patients without immune parameters (e.g. Walker *et al.*, 1997). Secondly, the review has been limited to those attempts which have involved relaxation and imagery training, often in combination with hypnosis. Excluded approaches are those which have involved a mixed intervention package where primary emphasis has been on cognitive stress management, such as administered to patients with cancer (Fawzy *et al.*, 1990) and HIV infection (Coates *et al.*, 1989; Antoni *et al.*, 1994); those solely using cognitive approaches such as disclosure of worries (Pennebaker, 1995); and conditioning studies (e.g. Kirschbaum *et al.*, 1992).

Studies will be briefly summarised with the aim of illustrating the diversity of intervention approaches regarding their nature and duration, the diversity of experimental designs, the diversity of immune parameters assayed and subject characteristics. The reports are structured as follows. Relaxation approaches will first be considered, which in aiming to alleviate stress induce a relaxed and passive cognitive attitude in the participant, whether they belong to healthy or vulnerable groups. Then, training that targets imagery of the immune system is reviewed. This requires an active and alert cognitive attitude in the participant who at the same time maintains a state of physical relaxation. Studies are then described involving healthy subjects experiencing a laboratory or real life stressor. This is followed by consideration of the value of hypnosis in moderating immune function. These themes are central to the design of the experiments of the author and colleagues that are briefly outlined. Two concern students receiving self-hypnosis training before exams, and the third, self-hypnosis training in patients with herpes simplex virus-2 (HSV-2). Inherent is the integration of dependent measures of immune function, well-being, as well as health. Following this, conclusions are drawn for directions in future research, for the importance of individual differences, and implications for neuropsychological connections, an unexplored field in human immunity research.

Relaxation: Invoking a Passive Attitude

Four investigators have examined single intervention approaches, all with some positive outcome for immunity. Subjects have included geriatrics, living alone in a residential facility (Kiecolt-Glaser *et al.*, 1985), oncology patients (Burns *et al.*, 2001), hypertensives (McGrady *et al.*, 1987a,b), and healthy participants (Green *et al.*, 1988). Kiecolt-Glaser *et al.* (1985) compared progressive muscle relaxation with social support or no-contact, with the intervention groups of the elderly, seen three times a week for a month. Only the relaxation group was found to show improvement in mood—a reduction in self-reports of distress—and this was accompanied by an up-regulation of immune function indexed by an increase in natural killer (NK) cell activity and a decrease in antibody levels to the herpes simplex virus (HSV). Importantly, the decrease in antibody levels persisted one month later despite a lapse in relaxation practice. Burns *et al.* (2001) found that sIgA in a mixed group of eight oncology patients, included in the second of a two phase meditative music relaxation and music improvisation programme, rose during the relaxation session having controlled for volume changes. There was no change in salivary cortisol, though this dropped when assessed at the beginning of the music improvisation session on the second day. Improvisation had no influences on the immune measures, and while there was a significant reduction in tension with music relaxation, this and other mood ratings did not correlate with the immune changes. McGrady *et al.* (1987a,b) compared two different relaxation approaches for effects on plasma cortisol concentration. These involved training in the self-regulation of physiological activity through biofeedback, and flotation in a tank with restricted environmental stimulation (REST). Both were successful in lowering cortisol. Green *et al.* (1988) examined immunoglobulins following daily relaxation practice for three weeks. Relaxation increased secretion rate of sIgA as well as serum rates of IgA, IgG and IgM, compared with controls.

Other studies have used mixed intervention programmes with the intent of maximising the likely impact of psychological factors. This is because of the absence of any clear understanding of the neurophysiological underpinnings of the various approaches to inducing relaxation, and accordingly any differential influences on the immune system which might lead to a more refined approach. The two studies with patient groups had promising outcomes for immunity, one with 13 patients with stage 1 breast cancer following radial mastectomy examined over 18 months (Gruber *et al.*, 1993), the other with asymptomatic men with HIV infection with CD4 counts below 400 (indicating a degree of immuno-suppression), examined over 20 weeks (Taylor, 1995). In cancer patients, the mixed intervention package involved EMG biofeedback, progressive muscle relaxation, letting go relaxation, and guided immune imagery, plus twice-daily home practice. In HIV patients, the intervention package consisted of

bi-weekly sessions of biofeedback/progressive muscle relaxation, hypnosis and meditation. The cancer patients were assigned either to the intervention or to a delayed intervention group who began treatment after 25 weeks, while the HIV patients were assigned to the intervention or to a control group.

In both studies, there was a favourable outcome for immunity. In cancer patients, this was found for a range of measures:—NK cell activity, peripheral blood lymphocytes, concanavalin A and mixed lymphocyte responsiveness, but not for immunoglobulin measures which on the whole were not altered. In HIV patients, the focus was on CD4 counts, which of all immune parameters, best mirrors symptomatic progression to AIDS. In the patients with breast cancer, the wide ranging benefits for immunity did not translate into psychological benefits, with only anxiety among a range of questionnaire measures showing a reduction, perhaps due to the more manifest nature of their illness. In HIV patients, the intervention was successful in elevating counts and this was accompanied by improvement in anxiety, mood and self esteem when compared with the control group.

Mixed intervention approaches of relatively short duration have been examined in two studies of healthy subjects evaluated for levels of stress. One study selected highly stressed subjects on the basis of the social readjustment scale of Holmes and Rahe and on the basis of low neutrophil activation (Peavey *et al.*, 1985). The subjects in the other study were medical students during their summer vacation, a time selected so as to avoid the pressures and stress of adaptation to medical school (an issue returned to later), and contrasting students, high and low on psychometric measures of stress assessed as a dependent variable (McGrady *et al.*, 1992).

Peavey *et al.* (1985) had a relatively successful outcome despite a somewhat brief intervention consisting of two weeks of daily home practice with physical and mental relaxation tape recordings accompanied by electromyography (EMG) and skin temperature biofeedback learned to criterion. Compared with the high stress control participants, the treatment group showed increased phagocytic activity of neutrophils, though white cell blood counts were unaffected, and there were improvements in levels of anxiety and coping ability. The training schedule of McGrady *et al.* (1992) consisted of only four sessions of EMG and skin temperature biofeedback which were combined with four weekly group sessions of relaxed breathing, progressive muscle relaxation and autogenic/imagery training; there was no home practice with audiocassette tapes. In the intervention group as a whole ($N = 14$) compared with a non-intervention control group ($N = 17$), there was an evidence of increased lymphocyte response to stimulation by mitogens, indicative of enhanced immune competence. There was also a reduction in neutrophils, responsible for a lowering of the total white blood cell count as lymphocyte number was unchanged. There was no effect on cortisol. However, when taking level of stress into account, the changes were found to be more pronounced in low stress subjects, casting doubt on the efficacy of the four-session intervention schedule. The reduction in neutrophils was interpreted as compatible with stress reduction, because neutrophil levels increase with bacterial infection, inflammatory processes and stress. Selye's (1955) general adaptation model of response to stress would characterise an alarm state, also at odds with a low state of stress. Accordingly, immune changes in low stress subjects do not fit easily with the authors' interpretation of the changes being an indicator of the alleviation of a state of stress.

Summary

The last study aside, there has on the whole been a successful outcome from a diverse range of relaxation interventions, whether applied singly or as part of a mixed programme, and involving a diversity of subjects including vulnerable groups such as geriatric, hypertensive and oncology patients, as well as healthy participants evaluated for stress. Typically, where more than single measures of immune function and well-being have been assessed, a patterned response has been obtained with some measures "improving" and others remaining unchanged. As yet the body of empirical evidence is limited, as is theoretical understanding, to permit more specific predictions about the nature of patterned psychological and immunological responses.

Immune Imagery and Active Cognitive Engagement

Training in guided imagery about immune function has been a popular technique, and has been incorporated with relaxation schedules. Once the participant has been placed in a state of deep relaxation, metaphorical images are invoked of a healthy immune system in a state of combat with invading viruses or germs. "Imagine friendly dolphins patrolling your blood stream gobbling up invaders." In children, the dynamics have been expressed through a puppet play (Olness *et al.*, 1989), whereas in adults, the narrative may be adapted to the nature of the patient's illness. The procedure was inspired largely on pragmatic grounds by work with oncology patients (Simonton *et al.*, 1978). Inherent in the approach was anxiety de-sensitisation based on classical Pavlovian conditioning principles. As in classical anxiety desensitisation behaviour therapy, by virtue of evoking illness-related images in a state of deep relaxation, there is a process of de-sensitisation to the stress of the illness and its impact on the body. Furthermore, as will be theorised here, the active cognitive engagement that is necessarily invoked by eliciting targeted imagery about immune system dynamics, will involve different neurophysiological processes than relaxation per se, with implications for brain-immune pathways. Conceivably, encouraging a more active cognitive attitude may also contribute to

differential effects on mood compared with the more passive imagery that accompanies relaxation training.

As will be seen, the outcome has on the whole been promising from studies with healthy participants, but in vulnerable subjects, aside from the author's study with patients with HSV-2 outlined below, the one other report has been disappointing from the perspective of immunity. Richardson *et al.* (1997) had assigned 47 women who completed treatment for primary breast cancer to either standard care, six weeks of imagery training, or additional social support. They found no differential effects on a range of immune parameters. On the other hand, there was a differential impact on mood and coping. Imagery training reduced stress and increased vigour and social and functional quality of life in comparison with the other groups. The psychosocial support group also disclosed advantages in overall coping and acceptance of death, while both interventions when compared with standard care shared improved coping skills and perceived social support.

Investigations with healthy subjects, all have involved imagery training assisted by music. Beneficial effects on sIgA in one study could not simply be attributed to music evoked imagery in itself (Rider *et al.*, 1990). Subjects were randomly assigned to a control group, or to two groups who listened for 17 min to imagery inducing music, or to the same music preceded by instructions about imagery of the immune system; the immune imagery group had been lectured on the immune system and the production of sIgA. Participants were instructed to practise at home, every other day for six weeks. sIgA was assessed at the beginning and end of the session before training, and similarly at weeks, three and six. There were advantages for both immunity and well-being for both relaxation approaches when compared with controls. Antibody production was higher and there were reductions in fatigue, tension and somatic symptoms of anxiety. However, sIgA was higher at weeks three and six with immune imagery than purely music, and the immune imagery group rated themselves as less confused–bewildered. The added advantages for immune imagery could not be attributed to group differences in vividness of imagery ratings. A longer training programme of 13 weeks was examined by McKinney *et al.* (1997) combined with a six week follow up. Salivary cortisol was the parameter used. When compared with waiting list controls, six weeks of training led to reductions in ratings of depression, fatigue and total distress. However, beneficial effects on cortisol which correlated with improvements in mood were not apparent until the follow up assessment.

These positive reports contrast with a wholly negative outcome by Zacharie *et al.* (1994), but here, there was a much shorter training period of only three weeks. Training consisted of comparing muscle relaxation assisted by music with relaxation immune imagery assisted by music, involving 30 min in the laboratory, weekly for three weeks together with daily home practice with an audiocassette. There were two studies. Dependent variables in one included monocyte chemotaxis (MC) and lymphocyte proliferative responses (LPR) to three mitogens and in the other NKC activity, all measured at the beginning and end of the sessions. They were unable to find any sustained systematic effects across three weeks, nor at a three week follow-up included in the second study. No relations were found between perceived stress and immune parameters.

Rider and Achterberg (1989) set out to demonstrate the putative importance of relations between the specificity of immune imagery and the specificity of changes in immune functions. They employed imagery that differentially targeted two different immune parameters, either total lymphocyte count or neutrophil count. Imagery training targeted either one. Participants were first given training in progressive muscle relaxation and in immune imagery which they were encouraged to draw. They were then given 20 min tape recordings which began with relaxation instructions, followed by the appropriate immune imagery and entrainment music, and then were instructed to practise at home, several times a week for three weeks. Predicted imagery-specific changes in immune function were disclosed, but were in the direction of a reduction in neutrophils and lymphocytes. The direction of change was puzzling and was hypothesised perhaps to reflect a systemic migration of leucocytes from the blood stream to tissues and lymphoid structures.

Within Session Changes

Immune changes have also been examined within sessions. For practical reasons, most have been restricted to salivary measures which are subject to confounding through increases in flow with relaxation. Commentary will be selective as most have involved a single session, having little to contribute to the efficacy of training programmes which require frequent practice to disclose reliable benefits on immunity and permanent changes in well-being, or have been uncontrolled, or have used small samples (Jasnoski and Kugler, 1987; Hall *et al.*, 1992a,b; 1996; Gregerson *et al.*, 1996). However, thoughtful design issues having implications for the field at large will be noted in passing in the single session report of Jasnoski and Kugler (1987) replicated by Gregerson *et al.* (1996). In recognition of the additional attentional demands of generating imagery of the immune system, they incorporated an alertness control group who carried out a vigilance task. They also controlled for individual differences in absorption, namely the ability to ignore distraction and become absorbed in experience, and so facilitate immersion in the imagery experience.

Only two reports have involved repeated assessment of within session effects. The best known is that of Olness *et al.* (1989) who demonstrated the importance of the specificity of immune imagery on sIgA in children. Children were randomised to three groups comparing a single session of self-hypnosis relaxation combined with non-specific immune related suggestions, self-hypnosis including specific suggestions about increasing salivary

immunoglobulins and a control group engaged in conversation. All had an initial orientation session with parents including a general relaxation tape to practise at home, a puppet play depicting basic immune system components, a saliva sample and a hypnotic susceptibility assessment with the Stanford Children's Hypnotic Susceptibility Scales. They returned two weeks later when further samples were taken at the beginning and end of a 25 min session. sIgA levels remained stable between sessions, but increased significantly in the group given specific imagery while remaining unchanged, both in the group with non-specific imagery and in the control group. sIgG levels were not altered. Hypnotic susceptibility was not associated with the effect, nor were ratings of interest and alertness. The results were replicated by Hewson-Bower and Drummond (1996) with 45 healthy children and 45 children with recurrent upper respiratory tract infections. While there was an increase in concentration of sIgA after both relaxation conditions, IgA/albumin ratio, a measure of local mucosal immunity, increased only with immune imagery. In both the healthy children and those with compromised health the increases in the two measures were associated with degree of rated relaxation.

The other study with repeated observations was the report referred to earlier which found no reliability between session changes in healthy subjects in two studies involving three weeks of immune imagery training assisted by music or progressive muscle relaxation assisted by music (Zacharie *et al.*, 1994). However, within session effects were observed in all three weekly sessions. In one study, there was a reliable reduction in LPR in both intervention groups, a change not seen in a control group included for one week only. In the second study, NKC activity decreased within sessions for all three groups, followed by a return to baseline an hour later, and with a slight increase following a mental stressor given at follow-up.

Summary

In conclusion, while the advantages of psychological interventions, including immune imagery training, on mood and well-being were unquestionable, advantages for immunity were less obvious. There were benefits for imagery training over and above other psychological interventions, benefits including coping skills, perceived social support, and enhanced meaning in life in breast cancer patients (Richardson *et al.*, 1997), and clear headedness in healthy subjects (Rider *et al.*, 1990). Unambiguous advantages for immunity were less easy to demonstrate. Cortisol secretion was reduced at a six week follow-up after six weeks of immune imagery training, a benefit validated through association with improvement in mood. But the effect was not evident at the end of six weeks of training and the relevance of imagery per se for this effect has not been tested (McKinney *et al.*, 1997). Examination of within session variation in immune measures demonstrated the plasticity of immune parameters, which aside from questioning the biological significance of up- and down-regulation raises the methodological desirability of retest reliability and replication.

Attempts to Moderate Influences of Stress

Johnson *et al.* (1996) examined 24 healthy participants for their response to a laboratory stressor after randomisation to relaxation training including hypnosis and progressive muscle relaxation or to a control group. A range of immunological and psychological parameters were collected along with blood pressure in a baseline condition and following three weeks of daily practice with audio-tapes of progressive muscle relaxation, alternating with hypnotic relaxation. Assessment on the first occasion included hypnotic susceptibility with the Stanford Clinical hypnotic induction scale followed by the Creative Imagination Scale (CIS) which is strongly correlated with hypnotic susceptibility. On the second occasion, the hypnotic induction was repeated for the relaxation group and both groups were then exposed to a role play stressor, after which the various measures were repeated. Mood assessment with the Hospital Anxiety and Depression Scale (HADS) showed that the relaxation group showed a reduction in anxiety whereas the control group showed an increase in depression. At three weeks, the Profile of Mood States (POMS) disclosed the relaxation group to be more composed, clearheaded, elated, confident, and energetic and they were more relaxed prior to the role play. Among the immune parameters assayed from serum and urine, the cytokine IL-1 showed reduced levels at three weeks in the relaxation group, whereas IgA levels increased, and while both groups showed a decline in mitogen response to PHA, the effect was stronger in the relaxation group. On the other hand, NKC activity declined only in the control group. In response to the stressor, the relaxation group showed increased responsiveness to PHA whereas responsiveness declined in the controls. The relaxation group also showed an increase in IL-1. Diastolic blood pressure fell in the relaxation group. Hypnotisability assessed by the CIS moderated the results by correlating with the increase in IgA following relaxation practice, while there were differential correlations with hypnotisability in the experimental and control groups in the post stress change in IL-1, positive in the relaxation group and negative in the control group.

The stress of exams in university students has been used as a naturally occurring stressor in two intervention studies (Kiecolt-Glaser *et al.*, 1986; Whitehouse *et al.*, 1996), an approach also adopted by the author which will be outlined subsequently (Gruzelier *et al.*, 2001a,b). Though a convenient stressor, it occurs against a background of academic stressors and peer pressures which as will be seen complicate interpretations of outcome.

Kiecolt-Glaser *et al.* (1986) compared with a control group, the effects of relaxation training on mood and immune function in first year medical students. The

intervention consisted of three weeks of relaxation training involving five group sessions of self-hypnosis, progressive relaxation, autogenic training and imagery exercises; a menu from which students could self-select in order to practise at home, prior to exams. NK cell activity and peripheral blood T lymphocytes were measured consisting of CD4 (helper/inducer) and CD8 (suppressor/cytotoxic) cells and the CD4:CD8 ratio. There were beneficial effects on mood such that the global distress score on a psychopathology symptom inventory and the obsessive–compulsive subscale were elevated at exam time for the control group but not for the intervention group. However, the advantages for the relaxation group did not translate to immune function in this study. This negative result may have occurred for a number of reasons. The type of relaxation procedure was not standardised but was deliberately left to the students' choices; this diversity of approaches may not have had homogeneous influences on immune function. There was also evidence of immune suppression for the group as a whole. The declines in NK cell activity, the CD4 percentage of total lymphocytes and CD4:CD8 ratio were from a baseline that the authors noted was at the bottom of the normal range. Notwithstanding, while the relaxation intervention did not buffer the decline in helper/inducer cells and NK cell activity, the amount of home practice did correlate positively with the percentage of CD4 cells. However, because frequency of practice was uncontrolled, interpretation is ambiguous for this advantage may be attributed to the relaxation training, to motivation, or to both factors.

Whitehouse *et al.* (1996) examined self-hypnosis/relaxation with 21 first year medical students over 19 weeks from the beginning of the academic year. There were four evaluations:- during orientation, late semester, the examination period, concluding with a post semester recovery assessment. Students were given 90 min weekly group training sessions aimed at practising relaxation and discussing their experiences. These included home practice which they were requested to do daily for 15 min. From the Harvard Group Scale of Hypnotic Susceptibility and the Inventory of Self-Hypnosis, which were administered in the first two group sessions, participants were found to be mainly in the medium and high susceptibility ranges. As in the Kiecolt-Glaser study, relaxation training preferentially lowered anxiety and distress, and there were no differences in immune function when comparing the relaxation and control groups. Unlike Kiecolt-Glaser's study, the exam period was accompanied by up-regulation of immune function including increases in B lymphocyte counts, activated T lymphocytes, NK cell cytotoxicity and PHA and PWM induced blastogenesis. The exam period also saw higher ratings of total mood disturbance, fatigue, loss of vigour, hostility, depression and obsessive-compulsive symptoms. Importantly, in this study ratings of the quality of the self-hypnosis, relaxation exercises predicted NK cell activity and cell number, though frequency of practice was unrelated to immune changes. The latter was, however, positively correlated with global measures of symptom severity during the exam and pre-exam assessments, which the authors interpreted as evidence that self/hypnosis relaxation was being practised with the intention of stress reduction.

In summary, the use of first year students may have reduced the chances of more demonstrable benefits for the psychological intervention. There was evidence on some scales of distress peaking at orientation (tension–anxiety, confusion–bewilderment) or to be as high at orientation as at exam time (two global distress scales and anxiety), or to be high throughout the semester until a fall during the post semester recovery (depression–dejection). This problem may also have compromised Kiecolt-Glaser's study, and can be inferred from Baker's (1985) assessment of immune function and mood in British medical students. Baker examined self report anxiety, CD4 counts and salivary cortisol, comparing changes in first year clinical students on their second day in a medical school new to them, with measures four months later, and with changes in second clinical year students assessed at the same time points. Changes in opposite directions on all measures were found between first and second year students. Measures were significantly higher on the first assessment in the first year students than in their second assessment and in the first assessment of second year students. Whereas second year students showed non-significant increases over the same period as exams approached.

Accordingly in the Whitehouse study when comparing the intervention and control groups, only limited benefits arose from relaxation training. This took the form of some reduction in anxiety and distress at exam time, though stress and fatigue rose for the cohort as a whole, a similar outcome as in the Kiecolt-Glaser study. In both investigations, the improvements in mood were not paralleled by immune changes that were distinguishable from controls. However, within the intervention groups in the Whitehouse study, the quality of self-hypnosis training was positively associated with immune up-regulation (NK cells), while in the Kiecolt-Glaser study, frequency of practice was associated with immune up-regulation (CD4 cells). These results suggest that psychological interventions practised in advance of a stressor may have potential value for enhancing mood as well as immune functions and preventing immune suppression triggered by the stressor, a promise to some extent fulfilled in two studies with self-hypnosis training below.

Hypnosis and Immune Function

Before outlining our investigations, which concentrated on self-hypnosis training with imagery as the sole intervention, the various studies with hypnosis will be drawn together. So far, hypnosis has been mentioned in the review in two respects. It has been used to assist with inducing relaxation and imagery training, and hypnotic susceptibility has been measured as an individual difference that may pre-dispose individuals to a more

successful outcome. From the perspectives of relaxation and immune imagery training, all the studies that have included hypnosis have tend to have a successful outcome.

As an intervention, it was included in the mixed approach of Kiecolt-Glaser *et al.* (1985) with the elderly and as one of a menu of options in her study of exam stress with medical students (Kiecolt-Glaser *et al.*, 1986). With elderly subjects, there was up-regulation of NKC activity and a decrease in antibody levels to HSV with four weeks of training. In students, the frequency of home practice over three weeks correlated with increase in the CD4% of total lymphocytes. However, conclusions about hypnosis cannot be drawn, given the mixed induction or menu approach. Whitehouse *et al.* (1996) used relaxation induced by hypnosis in a 19 week study from the beginning of term and found that the quality of self-hypnosis relaxation exercises predicted both NKC number and functional activity during medical student exams. In children Olness *et al.* (1989) found that two weeks of self-hypnosis training at home with specific immune imagery successfully increased sIgA in contrast to non-specific imagery. There is a further study of self-hypnosis, also with a positive outcome, Ruzyla-Smith *et al.* (1995) compared a rapid alert hypnotic induction, lasting only for up to 5 min and practised twice a day for a week, with two 1 h sessions of REST flotation and a non-intervention control group. Hypnosis led to higher B lymphocyte cell counts than flotation. T cell counts increased with both interventions, but only in high hypnotic susceptibility subjects. T cell subset analysis indicated that the beneficial effects of hypnosis were due to the CD4 helper T cells.

Turning to hypnotic susceptibility, there is evidence that high susceptibility is associated with more pronounced changes or even differential changes when compared with low susceptibility subjects. This was seen in the within session changes in NKC activity, MC and LPR with music assisted imagery training and music assisted progressive muscle relaxation, both without hypnosis itself (Zacharie *et al.*, 1994). It was also found in Ruzyla-Smith's study where in high susceptibility subjects increases in T cells were greater with both interventions—the two REST sessions with flotation and two weeks of rapid, alert self-hypnosis (Ruzyla-Smith *et al.*, 1995). Only in children in the study of Olness and colleagues was hypnotic susceptibility not predictive of immune up-regulation, perhaps due to the potential of children in general to become absorbed in experience. Absorption is highly correlated with hypnotic susceptibility, and classification on the basis of absorption showed advantages above for high scoring subjects in immune up-regulation with relaxation and alertness procedures by Gregerson *et al.* (1996) in replicating results of Jasnoski and Kugler (1987) who selected subjects for high absorption scores.

There is also evidence that hypnosis may facilitate mind–body influences on the immune system. Evidence that hypnosis may facilitate the modulation of immune function has perhaps been most extensively investigated in association with immediate and delayed responses in skin sensitivity to allergens. This has almost always involved suggestions of imagery of the immune system. Numerous affirmative results have been reported, yet at the same time, the phenomenon remains elusive (Locke *et al.* 1987; 1994). The array of studies, only one facet of hypnosis's influence on the skin, justifies a review to itself which space does not permit. Fry *et al.* (1964) provided one of the more comprehensive of the early studies. This was a two part investigation with 47 asthma patients with known skin sensitivity to house dust or pollen, unselected for hypnotisability and all but one naïve to hypnosis. In the first part, 18 patients were randomised to hypnosis or control groups and tested two weeks apart, the control group without hypnosis, and the hypnosis group, first without hypnosis and the second time with a hypnosis session, the last of three training sessions. Hypnosis included instructions to attenuate the skin reaction. Four strengths of allergen were administered bilaterally to the forearms. All were attenuated bilaterally to some extent with hypnosis, reaching significance with the two lower strengths. In the second part, the remaining patients were randomised into three groups, all of whom were given three sessions of hypnosis over two weeks but with different instructions:- bilateral non-reactivity, right arm non-reactivity or no immune-related suggestion. Compared with the baseline assessment, all groups showed attenuated reactions bilaterally. Successful localisation to one arm had been reported by Black (1963) the previous year, and subsequently was demonstrated by Zachariae and Bjerring (1990) who also successfully localised non-reaction to one arm through suggestion whereas the contralateral reaction was unaffected. Other successful attempts at attenuating reactions have been reported by Dennis and Philippus (1965) with antigens and histamine and Zacharie *et al.* (1994) with both immediate and delayed flares and wheals of Mantoux reactions. In contrast, Smith *et al.* (1992) failed with a group instructed to attenuate reactions, yet found that subjects could enhance reactions when instructed.

Laidlaw and her colleagues have shed some light on variability of response. In a first study, they examined five patients with asthma, all naïve to hypnosis training, for their flare and wheal sizes to histamine. These were recorded on six daily occasions within a two week period, three with hypnosis and three without and with order controlled (Laidlaw *et al.*, 1994a). Hypnosis attenuated flare but not wheal sizes bilaterally, and both reactions correlated with skin temperature; unilateral changes were not observed. They commented on wide individual variation between subjects in their small sample, as well as variation across sessions such that a day effect was highly significant. In a subsequent study (Laidlaw *et al.*, 1994b), the allergen reactions of 7 subjects were tested on 8 occasions without hypnosis and mood was assessed with the Profile of Mood States. In a discriminant function analysis, liveliness was found to account for 31% of the daily variance of wheal size. This was in the direction of the more lively the smaller the reaction, whereas

listlessness showed the opposite effect. In the light of what we have seen from the intervention studies above the influence of mood on the immune response makes sense. At the same time, the phenomenon of the modulation of the skin sensitivity response by hypnosis and the ability to restrict the control of the reaction by hypnosis to one limb, eludes reliable experimental control. In a further study, Laidlaw *et al.* (1996) found that hypnosis could be used to decrease skin reactivity to histamine. Thirty-eight participants undertook a control session to determine sensitivity to histamine and an intervention session during which they were invited to construct their own imaginative method of decreasing the size of the skin reaction and visualise this with hypnosis. Thirty two of the 38 subjects were able to reduce the size of their wheals to a highly significant degree, a result predicted by hypnotisability in the successful group. Mood ratings in the form of irritability and tension, and a change to higher blood pressure readings, were associated with less success.

In conclusion, there is a long history of the success of hypnotherapy as a stress reduction technique. There is evidence of its usefulness in enhancing psychological influences on the immune system and findings of preferential effects in hypnotically susceptible subjects.

Our chosen method of psychological intervention was self-hypnosis, not only encouraged by its apparent usefulness over other approaches for immune up-regulation but also encouraged by evidence at first hand of laboratory demonstrations of systematic neuro-psycho-physiological changes following the induction of hypnosis, which could not be attributed to psychosocial factors (for review see Gruzelier, 1998, 2000). This evidence, corroborated by others (e.g. Crawford and Gruzelier, 1992; Rainville *et al.*, 1997), gave added credence to the possibility of neuroimmunological effects.

THE EFFICACY OF SELF-HYPNOSIS IN MEDICAL STUDENTS AT EXAM TIME

We have examined in two investigations the efficacy of self-hypnosis relaxation training with immune imagery on the well-being and immune status of medical students experiencing exam stress, and in the replication study we included self-reported health around the exam period (Gruzelier *et al.*, 1998; Gruzelier *et al.*, 2001a,b). Our aims included the following. We standardised the interventions to single approaches to help clarify the processes involved and to promote a more homogeneous outcome regarding immune parameters. Our research also polarised around long-standing interests in individual differences in brain function, specifically hemispheric functional asymmetries (Gruzelier, 1989, 1999). When coupled with evidence of lateralised influences on the immune system, these have implications for personality differences that may be associated with immune competence. We predicted that cognitively activated students would respond advantageously to self-hypnosis training while withdrawn individuals would be less responsive. The background to these predictions will be considered in a final section on neurophysiology.

In the first investigation, a non-intervention control group was compared with a group receiving self-hypnosis instructions which encompassed physical relaxation, immune imagery and cognitive alertness. *In the second investigation*, a year later, a third group was added in order to elucidate the importance of the type of immune imagery. The procedures were approved by the Hospital Ethics Committee.

The subjects were predominantly second year medical students of both sexes ($N = 28$ and 31 in the first and second studies, respectively). Participants were given self-hypnosis training with an audio-tape recorded hypnotic induction for three weeks prior to exams. Though it is far from clear whether high hypnotisability may advantage imagery training (Hall, 1989; Olness *et al.*, 1989), as a safeguard in both studies, participants were first given a group screening with the Harvard Group Scale of Hypnotic Susceptibility (Shor and Orne, 1962). This is a behavioural scale which following a hypnotic induction assesses how well a subject responds to suggestions in order to determine to what extent hypnosis is present. These involve ideomotor suggestions, which if felt would lead to a motor response such as the hand falling down on the suggestion that it was heavy; response inhibition suggestions, such that a part of the body cannot be moved, so that a failure to move when challenged would be taken as evidence of hypnosis; and cognitive suggestions, such as positive or negative hallucinations or loss of memory, etc. On the basis of this, students were described as showing high or low susceptibility (in approximately equal numbers), but this was found in the first study not to influence the results. In the second study, subjects were allocated to immune imagery ($N = 11$) or to relaxation imagery ($N = 11$) or to control ($N = 9$) groups, balanced for hypnotic susceptibility. Immune and mood parameters were obtained during the exams, and either four weeks before the exams (before training) or after the exams. The subjects practised three times a week.

The hypnotic induction consisted of standard relaxation and deepening exercises following eye fixation and closure, instructions aimed at enhancing immune function, mobilising resources, and increasing energy alertness and concentration (after standard visualisation procedures and Banyai and Hilgard's (1976) active-alert hypnosis). In the second study, the relaxation imagery group instead received imagery of deep relaxation. Mood was assessed by the Speilberger state anxiety scale and by the Thayer activation–deactivation checklists (Speilberger *et al.*, 1970; Thayer, 1967). Subjects completed a life style questionnaire, and in the first study, the activated and withdrawn personality scales were administered.

Immune measures included counting lymphocyte subpopulations in blood samples by flow cytometry using fluorescently tagged specific cell surface markers (Gruzelier *et al.*, 2001a). The lymphocyte markers

TABLE I Group means and (standard deviations) for the immunological variables of high hypnotically susceptible ($N = 8$), low hypnotically susceptible ($N = 8$) and control subjects ($N = 12$) in baseline and university exam conditions. *indicates significant reduction ($p < 0.05$) at exams in controls not found with hypnosis. **indicates significant increase with hypnosis not found in controls

Immune measure	Hypnosis group					
	High susceptible		Low susceptible		Control	
	Baseline	Exam	Baseline	Exam	Baseline	Exam
CD3 μl	1897.12 (295.66)	1932.50 (537.52)	1909.87 (494.92)	1881.87 (377.66)	1913.33 (666.29)	1970.58 (530.59)
CD4 μl	1030.87 (272.08)	1010.37 (409.22)	1022.50 (392.51)	1004.12 (314.18)	1056.33 (376.94)	1040.83 (322.15)
CD8 μl*	481.88 (218.77)	522.75 (271.67)	578.88 (129.49)	613.38 (249.35)	662.67 (206.40)	555.08 (169.24)
CD19 μl	347.00 (211.28)	274.00 (145.84)	326.62 (117.35)	214.50 (58.60)	334.58 (112.50)	280.58 (151.49)
NKC μl*	211.88 (165.22)	239.38 (135.06)	177.75 (126.91)	195.13 (104.02)	266.92 (114.46)	177.33 (81.17)
Cortisol nmol/l**	300.00 (160.01)	387.50 (137.38)	363.63 (74.96)	408.25 (78.89)	365.50 (197.71)	349.00 (173.69)

included CD3, a protein involved in adhesion between lymphoid cells, particularly T cells and NK cells, and which is up-regulated when T cells are activated, CD4 (T-helper cells), CD8 (T-cytotoxic cells), CD19 (B-lymphocytes, which produce antibodies), and CD16 (NKC). Plasma cortisol was assayed by ELISA.

Unlike previous studies in the field, we showed an effect of hypnosis on circulating lymphocytes. In control subjects circulating NK and CD8, cell counts declined at exam time, and these declines were buffered by hypnosis (Table I; ANOVA: for NK cell counts $F = 6.03$, df $= 2, 25$, $p < 0.002$; for the ratio of CD8 to CD4 cells $F = 3.20$, df $= 2, 25$, $p < 0.059$). These effects were independent of changes in lifestyle and hypnotic susceptibility. However, individual differences in personality (in particular, the cognitive activation component from the activated personality scale) had a strong influence on increases in lymphocyte counts at exam time (Fig. 1).

Not surprisingly, the exams increased anxiety and tension ($p < 0.01$). However, participants receiving hypnosis showed an increase in "energy" at exam time ($p < 0.01$ vs. controls). NK cell counts at exam time correlated positively with energy ($r = 0.38, p < 0.05$) and negatively with anxiety ($r = -0.45$, $p < 0.02$). Furthermore, an increase in calmness with hypnosis was associated with an increase in CD4 cells ($r = 0.62$, $p < 0.01$; control group $r = 0.06$; Fig. 2), while B lymphocyte CD19 counts increased with anxiety at exam time ($p < 0.05$).

Interestingly, plasma cortisol concentration increased with hypnosis ($t = 2.09$, df $= 15$, $p < 0.05$), with no change in the control group. Furthermore, there were positive correlations between changes in NK cell counts and both changes in CD8 cells ($r = 0.52, p < 0.0004$) and cortisol ($r = 0.47, p < 0.01$). These suggest an integrated pattern of immune cell and hormonal changes. In keeping

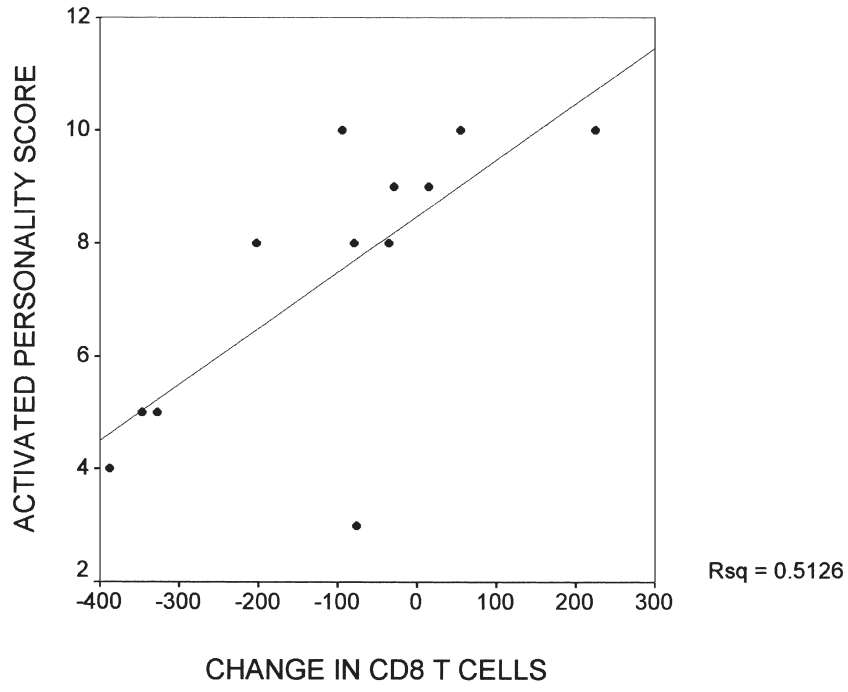

FIGURE 1 The correlation between the activated personality score and the change in circulating CD8 T-lymphocytes in controls from baseline to hypnosis (regression coefficient, $t = 3.24$, $p < 0.009$).

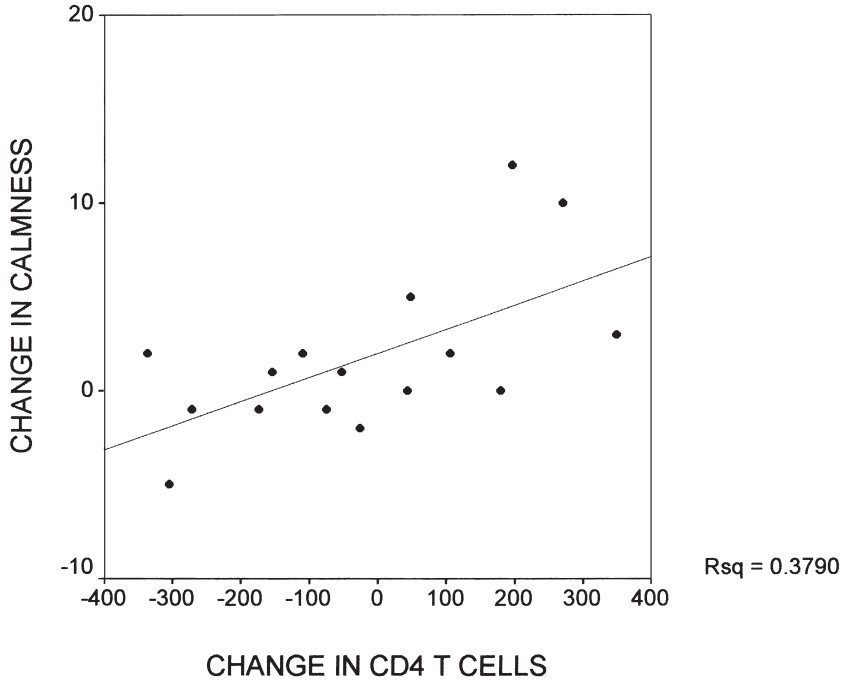

FIGURE 2 The correlation in high and low hypnotically susceptible subjects between the increase in calmness following hypnosis compared with baseline and the corresponding change in CD4 T-lymphocyte counts (regression coefficient, $t = 2.92$, $p < 0.011$).

with suppressive influences of cortisol on lymphocytes, there were negative correlations between cortisol and the counts of all the lymphocytes assayed, which themselves were highly inter-correlated ($p < 0.025 – p < 0.001$). Regarding the mood ratings, in the control group, plasma cortisol correlated positively with tiredness and anxiety at exam time ($p < 0.05$, $p < 0.001$, respectively), but not in the hypnosis group. Apparently, hypnosis may bring about a dissociation of the negative connection between cortisol and mood.

Turning to the personality differences, the cognitive activation scale predicted increases in lymphocytes at exam time (CD4, $r = 0.48$, $p < 0.03$; CD8, $r = 0.45$, $p < 0.03$; CD19, $r = 0.43$, $p < 0.04$). The correlation between the activated personality score and change in CD8 counts in controls, unmasked by hypnosis which elevated lymphocyte numbers, is shown in Fig. 1.

Results replicated in the second study included the buffering with hypnosis of the decline in controls in CD8 cells when expressed as a percentage of total lymphocytes (group × session, $F = 4.50$, df = 1, 25, $p < 0.05$). This was a highly reliable differentiation for individuals within groups (Chi Square (3)=13.15, $p < 0.004$). Alteration of the relation between cortisol and negative effect was shown by a negative correlation between the increase in cortisol at exam time and a reduction in tiredness following hypnosis ($r = -0.44$, $p < 0.04$) whereas there was a positive relation at baseline ($r = 0.40$, $p < 0.05$).

In answer to the question whether the type of imagery training was important, crucially it was only the training in imagery of immunity that was successful in buffering the decline in lymphocytes (Group × session interactions ($F(19) > 2.56$, $p < 0.03 – 0.06$), with the greater differentiation seen in CD3 and CD4 numbers whereby relaxation imagery failed to halt the stress-induced decline in lymphocytes:- total lymphocytes, $p < 0.008$; CD3, $p < 0.007$); CD4 $p < 008$; CD8, $p < 0.025$; CD19 < 0.042), whereas changes in lymphocytes with immune imagery were all non-significant. There were no significant changes in NK cells or cortisol.

Turning to the question about possible benefits on health, it was the CD4 lymphocyte that proved to be relevant to the health of the students in the second study (in the first study, too few students reported illnesses to evaluate the effect). In those who fell ill, there was a greater decline in CD4 counts (baseline mean 706.2, SD 231.3, exam mean 586.9, SD 161.3; $t(12) = 3.03$, $p < 0.01$), whereas in students remaining well, the decline was not significant. Importantly, fewer students in the immune imagery group fell ill—2/11 (18%) compared with 6/9 (67%) of the controls ($P < 0.001$) and 5/11 (56%) of those with relaxation imagery. The difference between the immune imagery and control groups was highly significant (Chi Square (19)=12.7, $p < 0.001$).

Aside from the importance of replicating findings in a field notable for disconfirmation of findings, of particular note was the finding in the second study that the buffering of the decline in CD4 counts was associated with whether or not students succumbed to viral infections during the exam period. Fewer students reported illnesses in the targeted immune imagery group than in the relaxation imagery and non-intervention control groups. These results boded well for the patient study in which the personality predictor was put to the test.

TABLE II Changes in recurrent genital herpes simplex virus and immune parameters pre- and post-hypnotherapy. Confidence intervals and *p* values are shown (CI is the confidence interval; NK, natural killer; LAK, lymphokine activated killer; ADCC, antigen dependent cellular cytotoxicity; HSV, herpes simplex virus)

	Pre	Post	Difference	95% CI	*P* value if significant (paired t-test)
Episodes in 6 weeks					
Responders	2.50	0.84	−1.66	−0.79– −2.51	0.001
Non responders	1.35	2.14	+0.78	0.08–1.48	0.033
Whole group	2.1	1.30	−0.80	−0.006– −1.59	0.048
Immune profile (cells/mm^3)					
CD3 cells	1252	1386	+133	22–244	0.021
CD8 cells	386	446	+59	11–102	0.019
CD4 cells	776	831	+55		
CD16 (NK) cells					
Responders	152	254	+112	23–201	0.019
Non responders	111	93	−18		
CD19 cells	219	227	+8		
Cortisol levels (nmol/l)	327	328	+1		
Functional immune activity (% cytotoxicity)					
Non-specific NK	41.67	44.48	+2.81		
HSV specific NK	6.82	7.21	+0.38		
HSV specific ADCC	16.09	16.56	+0.47		
HSV specific LAK in responders	11.36	29.8	+18.51	6.9–30.0	0.007
HSV specific LAK total	11.26	26.55	+15.2	2.8–27.7	0.022

THE EFFICACY OF SELF-HYPNOSIS IN PATIENTS WITH HERPES SIMPLEX VIRUS-2

Our patients suffered from (HSV-2), a form of genital herpes, which is a distressing condition often with a high recurrence rate and a high degree of stress. Typically, it coincides with persistently elevated levels of anxiety (Carney *et al.*, 1994), often profound psychosexual morbidity (Mindel, 1993) and compromised psychological well-being and quality of life (Goldmeier and Johnson, 1982). In reviewing evidence over a decade, Green and Kocsis (1997) observed that in many patients, the psychological impact of the disorder overshadowed the physical morbidity. In fact prior to the study, five patients reached the HADS threshold for pathological levels of anxiety and two reached the threshold for pathological depression, consonant with the distressing emotional effects of the infection. Furthermore, two patients had significant negative life events in the course of the study, a bereavement and a relationship breakup, reflected in subsequent pathological anxiety scores.

The experimental design was adapted from the student studies. The 21 patients were given six weeks of self-hypnosis training with an audio-tape recording following a live session. In the patient study, we used self-hypnosis with immune imagery as above. A baseline of recurrences was assessed over the six weeks prior to hypnotherapy. Immune parameters were assayed as above with the addition of functional NKC activity. Peripheral blood mononuclear cell (PBMC) non-specific NKC cytotoxic activity was measured in 18 h chromium release assays against K562 human erythroleukaemia cell lines. HSV specific NKC cytotoxic activity of PBMCs was measured using the human epithelial type 2 cell line (Hep-2) infected with HSV-1 24 h prior to the test. HSV specific cytotoxicity was also assessed following stimulation with interleukin-2 (termed LAK cell activity) as well as HSV specific antigen dependent cellular cytotoxicity (ADCC) following addition of autologous plasma. Psychometric measures consisted of the activation–deactivation checklist used in the above studies, the activated and withdrawn scales of the PSQ, while additional measures included the HADS.

We found that self-hypnosis reduced the recurrence of genital by 40% ($p < 0.05$) (48% when the two experiencing negative life events were excluded), and in 65% of patients (responders). The beneficial effect on health coincided with an enhancement in well-being. Hypnotherapy alleviated depression and there was a correlation between reduced anxiety and reduced frequency of recurrence ($p < 0.02$).

NKC function was up-regulated (Table II) and NKC numbers increased in responders ($p < 0.04$), but decreased in non-responders. Furthermore, functional NKC activity in responders showed significant enhancement in HSV specific NKC cytotoxicity ($p < 0.05$) and HSV specific cytotoxicity LAK cell activity ($p < 0.05$).

As in the study on medical students above, the activated personality scale measures, particularly the cognitive subscale, predicted immune up-regulation by hypnosis. In particular, there were correlations between activated personality and post-hypnotic changes in the measures of NKC function ($p < 0.05$), as shown in Fig. 3 depicting the charge from baseline to hypnosis in circulating NKC LAK activity.

Withdrawn personality was negatively associated with immune measures, that is in the direction of immune suppression with reduced NKC counts, and related predominantly to affective rather than behavioural aspects of withdrawal ($p < 0.005$). Similarly, the HADS scales of depression and anxiety disclosed associations with immuno-suppression, but these were with lymphocyte counts (CD3, CD4, CD8, CD19) and plasma cortisol, particularly after hypnosis. The relations were more consistent with depression than with anxiety.

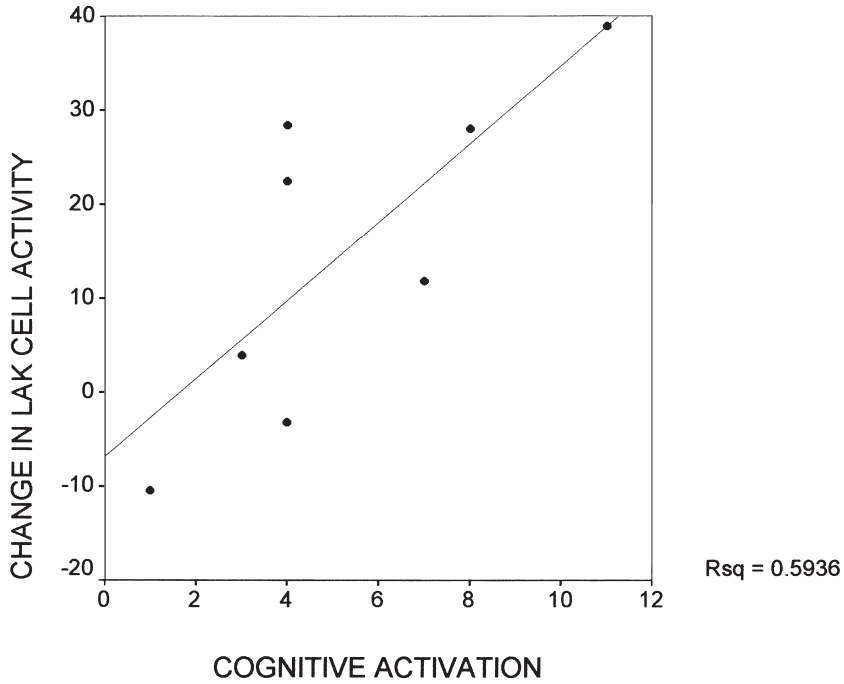

FIGURE 3 The change from baseline to hypnosis in circulating NKC LAK cell activity correlated with cognitive activation (regression coefficient, $t = 2.67$, $p < 0.018$).

In patients, hypnotisability was found to be associated with up-regulation of immune function and mood. Immune parameters included changes in NKC%, the post hypnosis CD8 count and baseline lymphocyte counts for CD3, CD4 and CD8 (negative correlations, $p < 0.05$). Mood parameters included reduction in tiredness ($r = 0.534$, $p = 0.02$) and depression ($r = 0.46$, $p < 0.05$). Importantly, cognitive activation correlated positively with clinical improvement ($r = -0.515$, $p = 0.02$); the higher the personality score, the fewer the herpes recurrences during the six weeks of hypnosis training. In view of the absence of correlations with baseline herpes frequencies, frequency of tape use and any difference in tape use between responders and non-responders, this relation could be interpreted as independent of motivation and other extraneous factors, and instead, a demonstration that cognitive activation predicted a better clinical response to hypnotherapy.

Summary

The benefits of self-hypnosis for health were confirmed by the striking results in the patients with HSV-2, extending the benefits for illness prevention in medical students at exam time. In support of mediational changes in the immune system, the reduction in herpes recurrences, which were almost halved by six weeks of training, was accompanied by functional enhancement in NKC activity in the form of HSV specific cytotoxicity and HSV specific cytotoxicity following stimulation with interleukin-2, along with an increase in NKC number. Furthermore, these beneficial changes were accompanied by improvements in mood and in clinical depression and anxiety. At one level, this was not surprising, given that the clinical outcome was visible to the patient. However, whether or not there was clinical improvement, well-being was enhanced and T-lymphocytes were up-regulated, indicating that there were general benefits from hypnotherapy independent of clinical response.

Individual differences in personality had a significant impact. Cognitive activation not only predicted immune up-regulation, as in the student study, but more importantly predicted herpes recurrence during hypnotherapy. Congruent with this relationship cognitive activation predicted functional enhancements in a range of NKC parameters, whereas in the student study, it correlated with the full range of T- and B-lymphocyte counts, but there was no relation with NKC counts. In the clinical study baseline, immune parameters also correlated with personality and pathological mood. There were positive correlations with cognitive activation, while there were negative correlations with withdrawal, especially its affective component, along with clinical depression and anxiety scales. Thus while both hypnotic susceptibility and frequency of practice were found to have an impact on the results, improvements in health were not restricted to high hypnotic susceptibles or to patients who practised frequently. More significant was the impact of personality differences in activation and withdrawal.

FUTURE DIRECTIONS

The review shows that a diverse collection of relaxation, imagery and hypnotic interventions alone or in combination has produced a range of changes in immune

function, not demonstrable in controls. Effects on the immune system have included changes in both cellular and humoral immunity, with measures of natural killer cell number and activation, antibody levels to the herpes simplex virus, cortisol secretion, neutrophil number and activation, lymphocyte number and activation, and salivary and serum immunoglobulins. Generally, the direction of at least some of the changes was congruent with immune function theory. At the same time, not all measures changed in consort, most commonly some were found to remain invariant. Furthermore, measures sometimes changed in a direction consistent with immune compromise or the outcome of re-distribution within and migration from the blood stream (McGrady *et al.*, 1992). It is recognised that there are fundamental questions about the functional significance of the direction of change of almost all immune parameters. This is because of the complexity of interrelations between such tightly integrated systems of checks and balances on immunity.

The complexity of stress is also poorly understood as shown by the seminal experiments of Selye (1955), who from examining the effects of stress on animals developed the concept of a general adaptation syndrome. This delineated functional influences of stress on the endocrine system that were bi-directional, with an initial increase in function characterising an alarm stage, followed by a gradual decline in function characterising a resistance stage, after which a stage of exhaustion was reached. In psychology, functional bi-directionality has been enshrined in the well-known inverted-U relation between stress and performance, but has seldom been alluded to in PNI investigations. One implication is that the direction of change in an immune parameter may differ according to the degree and duration of stress encountered and the natural history of exposure to stress. Accordingly, stressed subjects may disclose a reduction in a parameter with the psychological intervention through alleviation of Selye's alarm stage, or an increase in the same parameter in the resistance phase through recovery from suppression. In non-stressed subjects, an increase in an immune parameter may signify an enhancement of immune competence. It follows that it is unlikely that immune parameters respond to psychological interventions in the same way in healthy and vulnerable individuals. For these reasons, the impact of a therapeutic intervention on immune parameters by themselves, while of interest, is made more compelling by concurrent measures of well-being, and more so by measures of health.

Heterogeneity, Specificity and Validation

Methodological factors will be responsible for some of the heterogeneity of findings in this field. There is heterogeneity of subjects. Thus, participants have included patients with cancer, hypertension, HIV and HSV-2 infection and vulnerable groups such as the elderly and children, healthy subjects classified by rating scales as stressed versus non-stressed or facing stressful life events, or simply healthy volunteer subjects. Heterogeneity extends to the panoply of intervention techniques. These have included progressive muscle relaxation, biofeedback, flotation, self-hypnosis, autogenic training, relaxation through music, as well as imagery training which targets immune function, sometimes assisted by music. These cannot be presumed to have identical effects on neurophysiology and immune functions. Heterogeneity extends to training schedules that ranged from a single session to daily practice for 10 weeks or more, and the nature of the immune assay. The latter may involve the relatively benign collection of saliva or involve a stressful venepuncture.

Ambiguities about the direction of change in an immune parameter make validation through effects on other domains of measurement essential at this early stage of basic neuroscientific understanding. Most often immune changes have been accompanied by validation through mood ratings (Peavey *et al.*, 1985; Kiecolt-Glaser *et al.*, 1985; 1986; Rider *et al.*, 1990; Gruber *et al.*, 1993; Gregerson *et al.*, 1996; Whitehouse *et al.*, 1996; McKinney *et al.*, 1997; Gruzelier, 2001a,b). Beneficial effects have included reductions in ratings of global distress, anxiety, coping ability, fatigue, tension, depression, obsessive compulsive behaviour, and bodily symptoms of anxiety, and increases in energy and calmness. Though, improvements have tended to be restricted to isolated features of mood rather than global improvement. Occasionally, physiological parameters have provided validation such as EMG and skin temperature biofeedback learned to criterion (Peavey *et al.*, 1985; McGrady *et al.*, 1992). Now there are the beginnings of more conclusive clinical validation through benefits on health through the demonstration of improvement in a chronic illness, HSV-2 (Fox *et al.*, 1999) and suggestive evidence of illness prevention at times of stress in healthy people (Gruzelier *et al.*, 2001b).

Attempts at greater refinement or specificity will assist validation. These have included more standardised and homogeneous intervention techniques rather than mixed intervention packages, sometimes offered as a menu of opportunities. The strategy of varying one feature of an intervention while other components are held constant will assist with clarifying the processes involved. Interesting attempts have been made with imagery training to compare the outcome on immune parameters of targeting particular immune functions (Rider and Achterberg, 1989; Gregerson *et al.*, 1996). Specificity has been successfully demonstrated, though the meaning of the changes in terms of immune function has not been clear (Rider and Achterberg, 1989). Attempts at specificity have also included modification of skin sensitivity to allergens, and both attenuation and enhancement of reactions.

Replacing targeted immune imagery with relaxation imagery demonstrated that up-regulation of lymphocytes was preferentially influenced by immune imagery (Gruzelier *et al.*, 2001b). This supported suggestive evidence that targeted immune imagery may offer

advantages over and above other approaches whose main aim is relaxation (Olness *et al.*, 1989; Rider *et al.*, 1990; Gregerson *et al.*, 1996). Compatible with the requirement of alert, cognitive involvement in generating immune imagery, imagery training when compared with other relaxation approaches has been found to reduce confusion–bewilderment (Rider *et al.*, 1990), but has led to more anxiety and less calmness (Gregerson *et al.*, 1996). Fluctuations in mood have had demonstrable effects on modification through directed imagery on the size of the skin sensitivity reaction (Laidlaw *et al.*, 1994a).

Individual Differences

Heterogeneity confounds will also be reduced by investigation of individual differences. Historically, this has been exemplified by the phenomenon of hypnotic susceptibility, which underpins dramatic differences in abilities to respond to instruction and suggestion, and to relax and undergo cognitive changes. Importantly both cognitive and physiological flexibility has been ascribed to hypnotic susceptibility (Crawford and Gruzelier, 1992). For this reason, it has been assessed by many investigators in order to select subjects, high in susceptibility or in absorption which correlates highly with it (Jasnoski and Kugler, 1987), to stratify groups as high or low in hypnotisability (Zacharie *et al.*, 1994; Gregerson *et al.*, 1996; Gruzelier *et al.*, 2001a), or for purposes of correlation (Olness *et al.*, 1989; Whitehouse *et al.*, 1996; Gruzelier *et al.*, 2001a). In support of a propensity for dynamic changes Zacharie *et al.* (1994) found that it was highly susceptible subjects who demonstrated within session changes in NK cell activity and in lymphocyte proliferative responses, while Gregerson *et al.* (1996) found that it was high absorbers who increased their salivary IgA within session rather than low absorbers. Gregerson *et al.* (1996) also found that high absorbers scored highly on mindfulness-cognitive flexibility. We found that highly susceptible students increased their CD8% of total lymphocytes through imagery training more than low susceptibles (Gruzelier *et al.*, 2001a), while patients with herpes showed positive correlations with some baseline and post training lymphocyte counts, increases in NK cell% and functional activity, as well as with reductions in tiredness and depression (Gruzelier *et al.*, submitted). At the same time, hypnotic susceptibility is unrelated to the increase in sIgA within a single session in children (Olness *et al.*, 1989). Nor did we find hypnotic susceptibility relevant to the effects of 10 sessions of hypnosis, nine sessions of which were practised at home with a tape recording in our first student study (Gruzelier *et al.*, 2001a). Perhaps this is because hypnotic susceptibility, though possessing trait characteristics, is at the same time modifiable with practice, a commonplace clinical occurrence. Future research would benefit by re-examining hypnotic susceptibility at the end of training to determine whether susceptibility has in fact altered.

We doubt that the advantages observed for hypnotisability are non-specific, and occur as a result of relaxation, because of the differential effects shown in our comparative study between immune and relaxation imagery (Gruzelier *et al.*, 2001b). Some features of immune up-regulation were common to both, while others were specific to the targeted immune imagery training. This is in keeping with neuro-psycho-physiological studies in which some effects are independent of susceptibility and attributable to common experiences such as relaxation, while others are restricted to high susceptibles and by implication attributable to hypnosis (Gruzelier and Brow, 1985; Cikurel and Gruzelier, 1990; Raab and Gruzelier, 1994; Gruzelier, 2000; Williams and Gruzelier, 2001). The weight of evidence suggests that hypnotic susceptibility and its correlates of absorption and flexibility are important beyond the induction of relaxation *per se*. The advantages of training in guided imagery of the immune system were also apposite.

Cognitive Activation and Neurophysiological Pathways

Germane to this issue of specificity has been the predictive potential of the activated temperament and an action-orientated personality, particularly the cognitive activation component (Gruzelier *et al.*, 2001a; submitted). Historically, most research has focussed on individual differences accompanying immune compromise such as depression, loneliness and submissiveness (Schleifer *et al.*, 1983; Ramirez *et al.*, 1989; O'Leary, 1990; Bennett Herbert and Cohen, 1993; Zisook *et al.*, 1994). More recently, attention has turned to personality features associated with health and well-being such as hardiness, self-esteem, humour and expressing emotion rather than suppressing it (Valdimarsdottir and Bovbjerg, 1997; McClelland and Cheriff, 1997; Skevington and White, 1998; Fernandez-Ballesteros *et al.*, 1998; Doing and Bishop, 1999; Johnston *et al.*, 1999; Spiegal, 1999). Our results relating to the activated personality, which encompasses aspects of cognitive activation, behavioural activity and the expression of positive affect, extend the literature on individual differences in psychology related to immune up-regulation.

The construct of the activated personality first grew out of research on schizophrenia, and functional laterality. Active versus withdrawn syndromes were originally delineated by psychophysiological asymmetry parameters and subsequently were found characterised by a range of lateralised neuropsychological and psychophysiological processes in schizophrenia (Gruzelier, 1999 for review). Later, these syndromes were found to apply to personality dimensions in the normal population where they were also associated with opposite cognitive functional asymmetry patterns (Richardson and Gruzelier, 1994; Gruzelier *et al.*, 1995; Gruzelier, 1996; Gruzelier and Doig, 1996). Applicability to immune function follows evidence of lateralised influences on the immune system. This has

included evidence in animals. Dependent on the side of unilateral neocortical ablations in rodents, opposite effects have been found on IgG plaque forming cells and mitogen induced splenic T-cell proliferation; enhancement with an intact left hemisphere and compromise with an intact right hemisphere (Renouz *et al.*, 1983a,b; Neveu, 1993). NK cell activity has been impaired with left side ablation (Bardos *et al.*, 1981), and lower NK cell activity has been associated with left paw preferences (Betancur *et al.*, 1991). In man, a model has been proposed linking left handers, who as a group have a greater reliance on right hemispheric processing, with an increased incidence of autoimmune disorders (Geschwind and Behan, 1984; Geschwind and Galaburda, 1985; Lindsay, 1987). Reduced NK cell activity was found in nurses with a preferential right frontal EEG activation compared with those with the opposite asymmetry (Kang *et al.*, 1991).

The writer proposed an heuristic model incorporating evidence of lateralised influences on the immune system with hemispheric specialisation theory including associations with the left hemisphere of approach behaviour, positive affect and immune up-regulation and with the right hemisphere withdrawal, negative effect and immune down-regulation (Gruzelier, 1989). A test of the model was afforded by longitudinal assessment of asymptomatic men with HIV infection (Gruzelier *et al.*, 1996). Confirming the model, both EEG and neuropsychological asymmetry patterns assessed at study onset were predictive of CD4 counts two to three years later; participants with a left hemispheric functional preference on first assessment had higher counts than those with a right hemisphere functional preference and vice versa. Subsequently, Clow and colleagues have reported theoretically consistent asymmetries in sIgA and free cortisol concentration following lateralised trans-magnetic stimulation of temporo-parietal occipital cortex (Gruzelier *et al.*, 1998; Evans *et al.*, 2000).

The activated temperament, cognitive activation in particular, versus withdrawal relates to left and right hemispheric specialisations in the form of approach versus avoidant behaviour (and hence the chosen descriptors activated and withdrawn), and hemispheric specialisation relates to positive versus negative affect. The particular relation here between immune function and the active syndrome subscale active speech, which describes speaking and thinking quickly, provides compelling support for the association of immune up-regulation with left hemisphere functional preference, given the unambiguous left hemisphere involvement in speech production. There are clear links between the activated personality dimension and fighting spirit, laughter and exercise, which have demonstrable advantages for immune function (Greer, 1983; Valdimarsdottir and Bovbjerg, 1997; Skevington and White, 1998; Fernandez-Ballesteros *et al.*, 1998).

Finally, aside from its predictive validity, the activated versus withdrawn personality dimensions provide insights into the neurophysiological basis of mechanisms mediating psycho-neuro-immunological influences. It follows that the activated personality dimension, with its neurophysiological validation, may help in clarifying individual differences in psycho-neuro-immunological mechanisms. Guidance for individual differences in patient response and compliance may follow the predictive ability of the personality trait. Hypnosis training may succeed better in a depressed patient with the active syndrome trait (showing the potential for modification), in contrast to a depressed patient with a withdrawn personality trait. It also makes sense of why directed imagery of the immune system, with its active, cognitive requirement when compared with the more passive imagery of relaxation training, appears the more successful form of intervention.

CONCLUSION

Research on clinical interventions in this field of psycho-neuro-immunological research is very much in its infancy. As evinced by the nature of the experimental designs of most studies, investigations have been carried out with meagre resources by dedicated pioneers. Typically, there has been a small number of training sessions, sometimes just one, and typically a small number of immune parameters, which have been assayed once or twice, seldom more frequently. Nonetheless, the conviction of pioneering researchers that psychological interventions may benefit health through influence on the immune system and well-being is being vindicated. The body of evidence reviewed here, when seen in conjunction with the greater accumulation of evidence from studies focussing simply on relations between immune compromise and stress, justify a larger investment of time and funding, not only in basic cognitive and immunological science in order to elucidate the mechanisms involved, but also in formal evaluation of clinical intervention strategies.

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