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EDITORIAL COMMENTARY

In the first instance we draw attention to the change in instructions to authors such that *Contemporary Hypnosis* has for some years relaxed its word limit on regular articles to allow more considered theoretical contributions and reviews, as seen in the continuing series on the nature of hypnosis with contributions including those Wagstaff, Gruzelier and Berrios. The same policy is now being applied to experimental papers, with an upper limit of 6000 words excluding references. The Board also particularly wishes to encourage clinical case studies and reports.

The present issue is the first for some time without case studies. However, the first two papers deal with clinical issues. The first concerns individual differences in personality in relation to self-hypnosis training in patients with chronic, virulent genital herpes. This study, though preliminary, had a positive clinical outcome reducing reoccurrence by almost half and at the same time increasing cytotoxicity of natural killer cells (NKC) to the herpes virus. A cognitively activated personality was associated with a profile of immune system up-regulation in lymphocytes and NKC activity. Withdrawal and introversion were associated with immune compromise. Hypnotizability was associated with reduction in depression and also shared with frequent practice positive associations with immune system up-regulation. In the second paper Page and Green report encouraging evidence from a survey of practitioners that recommendations to avoid negative after-effects of hypnosis are to a large extent being followed in the USA.

We publish Theodore Sarbin's invited address to the American Psychological Association in August, 2002. In this address contributions of Ernest Hilgard, Martin Orne and Nicholas Spanos are seen as a scientific dialogue about whether hypnotic behaviour is involuntary or voluntary, an issue held to be central to understanding hypnosis, as is the role of assigning meaning to self-reported experience. Another perspective, sympathetic to Sarbin, is found in the experimental report of Gorassini. He demonstrates outside of hypnosis that the instructed prior action, arm raising, may prime and facilitate response to suggested arm raising when it is contrasted with a condition involving instructed inaction. Finally an electrophysiological report contributes to the growing body of evidence of alterations of frontal function following instructions of hypnosis. These alterations follow very different dynamics in participants scoring high and low on hypnotic susceptibility, with contrasting functional implications.

A review is provided of the new *International Handbook of Hypnosis* emanating from Australia.

John Gruzelier
Editor

INDIVIDUAL DIFFERENCES IN PERSONALITY, IMMUNOLOGY AND MOOD IN PATIENTS UNDERGOING SELF-HYPNOSIS TRAINING FOR THE SUCCESSFUL TREATMENT OF A CHRONIC VIRAL ILLNESS, HSV-2

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Abstract

Individual differences in personality, in particular cognitive activation, withdrawal and hypnotic susceptibility were examined in a study of self-hypnosis training in patients with chronic and severe herpes simplex virus (HSV-2), genital herpes, along with depression, anxiety and activation ratings. Immune parameters were assayed before and after the six-week training. Self-hypnosis almost halved recurrence rate, benefiting 65% of the patients. Furthermore clinical responders demonstrated an increase in natural killer cell (NKC) cytotoxicity of herpes infected cells as well as up-regulation of non-specific immune parameters. In replication of a student exam stress study (Gruzelier, Smith, Nagy and Henderson, 2001a) cognitive activation was positively associated with immune function; with improvement in herpes recurrence, improvements in specific NKC cytotoxicity, baseline functional NKC activity and energy ratings, and was unrelated to frequency of practice. No other measure of personality or affect was associated with immune system up-regulation and improvements in health. Depression and, to a lesser extent, anxiety improved independently of herpes outcome. Depression and/or anxiety at baseline were positively associated with withdrawal, particularly the affective aspects, and neuroticism, which were associated with immune down-regulation seen in NKC counts and NKC functional activity at baseline. Hypnotizability was associated positively with aspects of immune system up-regulation and negatively with clinical depression. Immune system up-regulation in clinical responders correlated positively with frequency of self-hypnosis practice. This is possibly the first evidence for the efficacy of self-hypnosis training for a chronic medical illness. Evidence (1) of the benefits to health and (2) of the viral specificity of the immune changes, here in the form of increased cytotoxicity of NKC for cells infected with the herpes virus, gives credence to the value of a psychological intervention for immunity; evidence for which is scarce in the field of psychoneuroimmunology. The predictive ability of cognitive activation for response to hypnotherapy is in keeping with the preferential effects on both immune parameters and health of hypnosis instructions which require the generation of dynamic imagery in contrast to instructions of passive relaxation imagery (Gruzelier, Levy, Williams and Henderson, 2001b).

Key words: self-hypnosis, herpes, personality, cognitive activation, hypnotizability, immunity, mood

Introduction

The emergent field of psychoneuroimmunology (PNI) grew out of the wealth of evidence of psychological influences on immunity, particularly anxiety, depression and stress (O'Leary, 1990; Bennett Herbert and Cohen, 1993; Leonard and Miller, 1995; Evans, Hucklebridge and Clow, 2000; Ader, Felten and Cohen, 2001). Then followed more limited evidence of the benefits for immunity and health from psychological interventions that reduce stress and anxiety and alleviate depression (see for review Gruzelier, 2002a, 2002b). Anxiety, depression and stress all represent negative emotions. For this reason individual differences in immunity have typically focused on personality features that accompany immune compromise such as depression, loneliness and submissiveness (Schleifer, Keller, Camerino, Thornton and Stein, 1983; Ramirez, Craig et al., 1989; O'Leary, 1990; Bennett Herbert and Cohen, 1993; Zisook, Sucter, Irwin, Darko, Sledge and Resovsky, 1994). Only more recently has attention turned to positive personality features associated with health and well-being. These features have included liveliness, hardiness, self-esteem, humour, expressing emotion rather than suppressing it, possessing a fighting spirit (Laidlaw, Booth and Large, 1994; McClelland and Cheriff, 1997; Valdimarsdottir and Bovbjerg, 1997; Fernandez-Ballesteros, Ruiz and Garde, 1998; Skevington and White, 1998; Johnston, Earl, Giles, McClenahan, Stevens and Morrison, 1999; Spiegel, 1999) and, in our own investigations, cognitive activation (Gruzelier, Clow, Evans, Lazar and Walker, 1998; Gruzelier et al., 2001a).

Hypnotic susceptibility and associated personality features such as absorption have also received some recognition, particularly in intervention studies. Hypnotic susceptibility may underpin often dramatic differences in the ability to respond to instruction and suggestion, and to relax and undergo cognitive changes. Importantly both cognitive and physiological flexibility have been ascribed to hypnotic susceptibility (Crawford and Gruzelier, 1992; Gruzelier, 2002c). Regarding immunology Zachariae, Hansen, Andersen, Jinquan, Petersen, Simonsen, Zachariae and Thestrup-Pedersen (1994) found that it was the high hypnotically susceptible individuals who demonstrated within-session changes in NK cell activity and in lymphocyte proliferative responses. Similarly in a study where absorption was positively associated with mindfulness-cognitive flexibility ratings, Gregerson, Roberts and Amiri (1996) found that participants with high absorption scores increased their salivary S-IgA within session more than low scorers. Ruzyla-Smith, Barabasz and Warner (1995) found that subjects with high hypnotic susceptibility scores increased CD4 T cell counts both as a result of two restricted environmental stimulation sessions with flotation, or after two weeks of rapid, alert self-hypnosis. Following imagery training with hypnosis high hypnotically susceptible students increased their CD8 T-lymphocyte percentage more than low scoring students (Gruzelier et al., 2001b). For these reasons, investigators in psychological intervention studies have often selected subjects who are high in hypnotic susceptibility or absorption (Jasnowski and Kugler, 1987), have stratified groups according to levels of hypnotizability (Zachariae et al., 1994; Gregerson et al., 1996; Gruzelier et al., 2001b), or have correlated outcome with hypnotizability (Olness, Culbert T and Den, 1989; Whitehouse, Dinges, Orne, Keller, Bates, Bauer, Morahan, Haupt, Carlin, Bloom, Zaugg and Orne, 1996). At the same time in some studies hypnotic susceptibility has been found to be unrelated to immune system up-regulation, both in children (Olness et al., 1989) and in university students after three weeks of self-hypnosis training (Gruzelier et al., 2001a), perhaps because hypnotic susceptibility, though possessing trait characteristics, is at the same time modifiable with practice (Diamond, 1989).

Of central relevance to the present report was the fact that in a study with university students (Gruzelier et al., 2001a) it was found that the personality dimension, cognitive activation, was a strong predictor of immune system up-regulation following self-hypnosis training. Here, the replication of this relation in a study of the efficacy of self-hypnosis training in patients with a chronic viral infection was attempted. As similar hypnosis protocol and immune assays were used, the results of the student study are briefly reviewed. Twelve control students were compared with 16 who were trained with three weeks of self-hypnosis training before exams, standardizing frequency of practice in order to avoid the potential confound of motivational differences in practising hypnosis. Hypnosis involved instructions to evoke immune imagery, physical relaxation and cognitive alertness. The immune assay was repeated twice, before training and during the exams, and included natural killer cell (NKC) counts, cortisol, and counts of CD3+, CD4+ and CD8+ T-lymphocytes, and the B-lymphocyte CD19+. Following considerations of lateralized influences on the immune system, such that a left-lateralized active, action-orientated and cognitively alert personality would be associated with immune system up-regulation, while a right-lateralized withdrawn personality would be associated with down-regulation (Gruzelier, 2002c), personality was measured with the Activated and Withdrawn scales of the Personality Syndrome Questionnaire (PSQ). Mood was measured with the Spielberger anxiety and Thayer activation scales.

As has been well documented (Kiecolt-Glaser, Spiecher, Holliday and Glaser, 1984; Glaser, Kiecolt-Glaser, George, Spiecher and Holliday, 1985; Halvorsen and Vassend, 1987; Deinzer and Schuller, 1998), NKC counts and CD8+ lymphocyte counts were found to decline in controls with the stress of exams. Importantly the decline in these measures, both of which have the ability to lyse infected cells, did not occur following hypnosis, an advantage which was independent of life-style changes at exam time. Additional benefits for hypnosis included higher Thayer Energy ratings at exam time, which correlated positively with NKC counts for the group as a whole and in turn correlated negatively with Spielberger Anxiety. Increases in calmness ratings following hypnosis correlated positively with increases in CD4+ counts. In a follow-up study (Gruzelier et al., 2001b) the same hypnotic instruction was contrasted with another instruction which replaced immune imagery with imagery of deep relaxation. Again hypnosis buffered the decline in CD8+ cells and the CD8+ ratio relative to CD4+ cells, but this was particular to the group with the immune imagery, confirming results found by Olness et al. (1989) with S-IgA in children, with the greater differentiation here seen in CD3+ T cell numbers. Regarding personality, compelling relations were found with T- and B-lymphocyte up-regulation. Cognitive activation correlated positively for the group as a whole with the full range of lymphocytes assayed: CD3+, CD4+, CD8+, CD19+, as well as with all the lymphocyte counts at exam time. This was despite the fact that by elevating lymphocyte numbers the hypnotic intervention would be expected to mask this relation; indeed correlations between cognitive activation and lymphocyte counts were of higher statistical significance in the non-intervention control group. No correlations in that study were found between personality and NKC number or cortisol.

Reported here is the application of the self-hypnosis training protocol to patients with a chronic and severe viral illness, herpes simplex virus-2 (HSV-2), genital herpes. Of critical importance to immunological science given the ambiguity about the significance of the various measures of up- and down-regulation, credence for the salience of changes in immunity is strengthened by (1) showing benefits for health and (2) demonstrating changes in immune parameters that are relevant to the illness under study. This has been largely absent from the PNI field. It was possible to satisfy the first criterion in the

student exam stress replication study (Gruzelier et al., 2001b) whereby eight students reporting illnesses around the exam period displayed a highly significant decline in CD4+ counts, which was not found in the well group. Furthermore, fewer students in the immune imagery group fell ill – 2/11 (18%) compared with 6/9 (67%) of the controls and 5/11 (56%) of those with relaxation imagery. The difference between the immune imagery and control groups was highly significant. Importantly in the patient herpes study there was an opportunity to test both criteria by examining on the one hand reduction in herpes recurrence rate and on the other by examining functional NKC activity for cytotoxicity for herpes infected cells.

HSV-2 is a distressing condition in which Green and Kocsis (1997), from a review of evidence over a decade, observed that the psychological impact of the disorder overshadowed the physical morbidity in many patients. The disease is accompanied by persistently elevated levels of anxiety (Carney, Ross, Bunker, Ikkos and Mindel, 1994), often profound psychosexual morbidity (Mindel, 1993) and compromised psychological well-being and quality of life (Goldmeier and Johnson, 1982). An association between psychological distress and reduced resistance to HSV was first reported by Lycke, Norrby and Roos (1974), when depressed patients were found to possess increased antibodies to the latent HSV, Epstein-Barr virus and Cytomegalovirus. Subsequently reduced resistance to HSV was found in association with negative affect in medical students at exam time and in spouses about to divorce, while coincidentally there was a reduction in NKC activity, CD4+ lymphocyte counts and lymphocyte proliferative responses (see Sheridan, Dobbs, Brown and Zwilling, 1994). NKC, macrophages, CD4+ and CD8+ lymphocytes, INF α and INF γ , IL-2 and leucocyte migration inhibitory factor all protect against HSV (Rinaldo and Torpey, 1993). HSV patients therefore presented a highly suitable opportunity to replicate the findings of the student study and to examine both positive and negative personality influences on health and immunity as a result of self-hypnosis training. The results on viral recurrence and immunity were first published in a virology journal (Fox, Henderson, Barton, Champion, Rollin, Catalan, McCormack and Gruzelier, 1999) and are briefly reviewed here for the hypnosis readership.

Method

Patients

Patients attended the Department of Genitourinary Medicine at Chelsea and Westminster Hospital. The 21 chronic patients had frequently recurrent genital herpes and were due to discontinue prophylactic antiviral medication for a trial period or were reluctant to take the medication. None were HIV seropositive. Their median age was 36 years (ranging from 23 to 64 years), 65% were female, the median duration of rgHSV in years was 10 (ranging from 1 to 26 years), while the median number of annual recurrences was 12 (ranging from 6 to 25). Consonant with the distressing emotional effects of the infection, prior to the study five patients reached the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) threshold for pathological levels of anxiety and two reached the threshold for pathological depression. During self-hypnosis training two patients had significant negative life events, a bereavement and a relationship breakup. This was mirrored in their HADS Anxiety scores where both exceeded the threshold for pathological anxiety in their post-hypnosis assessment, whereas they had been below threshold prior to hypnosis. These two patients were excluded from some treatment analyses as indicated.

Immunology

The same immune parameters were assayed as in the previous studies above (Gruzelier et al., 2001a, 2001b) with the addition of a wide range of functional NKC activity measures. Peripheral blood mononuclear cell (PBMC) non-specific NKC cytotoxic activity was measured in 18h chromium release assays against K562 human erythroleukemia 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 24h prior to the test. The background responses obtained with uninfected Hep-2 cells were subtracted from those obtained with HSV infected Hep-2 cells. HSV-1 was used because HSV-2 is known to be cytopathic for Hep-2 cells and because HSV-1 infected cells have been used successfully to analyse the immune responses to both HSV-1 and HSV-2. 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.

Individual differences

Psychometric measures consisted of the Thayer activation-deactivation checklist (Thayer, 1967) used before together with the Activated and Withdrawn scales of the Personality Syndrome Questionnaire (PSQ) (Gruzelier, Jamieson, Croft, Kaiser and Burgess, 2002). Additional measures included the HADS and the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975). Hypnotic susceptibility was measured with the Barber Suggestibility Scale (Barber and Wilson, 1969) with Subjective and Objective subscales administered in an hypnotic context. The mean score was 4.8 (responders 5.1, non-responders 4.3).

Design

The experimental design was adapted from the student studies. Patients were examined in two cohorts at baseline and after a six-week course of self-hypnosis. After a group hypnosis session they were given self-hypnosis cassette recordings to take home and were recommended to practise a minimum of three times a week, a total of 18 times; the mean was 17 sessions, ranging from 3 to 33 sessions, with one additional patient excluded through non-compliance. Hypnosis involved instructions of relaxation, immune imagery, cognitive alertness and ego strengthening, as for the original student study (Gruzelier et al., 2001a). A baseline of herpes recurrences was assessed over the six weeks prior to hypnotherapy, and then throughout the six weeks of training. Recurrences were recorded in a diary. Psychometric assessment took place at the beginning of the study.

Analysis

A priori predictions about relations between personality, mood, health and immunity were tested with Pearson correlations. Correlations were also examined with hypnotizability and frequency of practice. As attrition due to damage to the assay of functional NKC measures post-hypnosis reduced the available assays and compromised the use of repeated measures ANOVA, in order to ensure consistency across variables, changes in responders and non-responders were examined with paired *t* tests. The sample size was reduced for correlations with changes in functional NKC parameters and with post-hypnosis but not baseline measures.

Results

The effect of hypnosis on the frequency of HSV-2 recurrence

The crucial test as to whether self-hypnosis training would benefit illness was answered affirmatively. Self-hypnosis had a marked effect in reducing the recurrence of genital herpes. The number of recurrences fell with hypnosis by 40% ($t=2.109$, $df=19$, $p=0.048$) reaching 48% ($t=2.673$, $df=17$, $p=0.016$) with the exclusion of two patients who experienced stressful life events in the course of the six-week intervention. This result was all the more significant when it was considered that the patients suffered severe, chronic illnesses with high recurrence rates. Thirteen patients (65%) showed a reduction in recurrences and were termed responders. Non-responders, who included the two with life events, either reported no change (4) or an increase in recurrences (3). The median number of occurrences in the six weeks before hypnotherapy was 2 (range 0–6) and during the six weeks of self-hypnosis was 1 (range 0–3). Improvements could not be explained away on the basis of demographic or clinical factors, hypnotic susceptibility or frequency of practice. The results are shown in Table 1. In fact non-responders tended to practise more, perhaps due to their visible lack of improvement in herpes recurrence. Though positive, correlations did not reach significance between the reduction in occurrences and either practice ($r=0.246$, $p=0.322$) or hypnotizability ($r=0.317$, $p=0.215$).

Hypnosis and immunity

The results of the immune variables are shown in Table 1. Regarding NK cells there was a significant increase in numbers in responders ($t=2.42$, $df=12$, $p=0.032$) whereas non-responders on average showed a fall. There was a highly significant inverse relation between baseline and post-hypnotic non-specific NKC activity ($r=-0.897$, $p<0.001$), perhaps indicative of a law of initial values effect. Of particular importance for immunological theory there was evidence of alterations in functional NKC cytotoxicity particular to the herpes virus. Responders showed significant increases in both HSV specific NKC cytotoxicity ($t=2.48$, $df=6$, $p=0.048$) and in HSV specific cytotoxicity following stimulation with interleukin-2 (termed LAK cell activity) ($t=2.45$, $df=7$, $p=0.044$).

Lymphocytes increased for the group as a whole: CD3+ cells ($t=2.55$, $df=16$, $p=0.021$), CD8+ cells ($t=2.62$, $df=16$, $p=0.019$), with a non-significant increase in CD4+ cells ($p=0.104$). As the increase in lymphocytes occurred independent of illness outcome, this represented a non-specific effect of the psychological intervention on immunity.

Of importance to the practice of self-hypnosis, there was a tendency for frequency of practice to be correlated positively with immune system up-regulation in both specific and non-specific measures. This was shown by the increases in NKC numbers ($r=0.536$, $p=0.054$), CD8+ cells ($r=0.50$, $p=0.05$), HSV specific NKC cytotoxicity ($r=0.965$, $p<0.035$) and HSV specific LAK activity ($r=0.934$, $p=0.066$) (the numbers of patients are reduced because of attrition).

Hypnosis and affect

Means and standard deviations of HADS Anxiety and Depression scales for the 13 responders and the five non-responders, having excluded the two with negative life events were as follows: Anxiety, Baseline 9.69 (3.95), Post 7.17 (5.97); Depression, Baseline 5.31 (4.31), Post 2.92 (3.68). Non-responders: Anxiety, Baseline 8.20 (3.35), Post 6.80 (3.03); Depression, Baseline 3.00 (1.87), Post 1.00 (0.71). The means show that there was a reduction in HADS Anxiety and Depression for both responders and non-responders. At the same time there was little change on the checklists of tension, tiredness, energy and calmness completed at the time of the blood draws.

Table 1. Changes in recurrent genital herpes simplex virus and immune parameters pre and post hypnotherapy together with confidence intervals and *p* values

	Pre	Post	Difference	95% CI	<i>p</i> value if significant (paired <i>t</i> -test)
<i>Episodes in six weeks</i>					
Responders	2.50	0.84	-1.66	-0.79 to -2.51	0.001
Non-responders	1.35	2.14	+0.78	0.08 to 1.48	0.033
Whole group	2.10	1.30	-0.8	-0.006 to -1.59	0.048
<i>Immune profile (cells/mm³)</i>					
CD3 cells	1252	1386	+133	22 to 244	0.021
CD8 cells	386	446	+59	11 to 102	0.019
CD4 cells	776	831	+55		
CD16 (NK) cells					
Responders	152	254	+112	23 to 201	0.019
Non-responders	111	93	-18		
CD19 cells	219	227	+8		
Cortisol levels (nmol/l)	327	328	+1		
<i>Functional immune activity (% cytotoxicity)</i>					
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	29.80	+18.51	6.9 to 30.0	0.007
HSV specific LAK total	11.26	26.55	+15.2	2.8 to 27.7	0.022

CI = confidence interval, NK = natural killer, LAK = lymphokine activated killer, ADCC = antigen dependent cellular cytotoxicity, HSV = herpes simplex virus

HADS Depression decreased significantly for patients as a group (Group: $F=5.71$, $df=1,15$, $p=0.030$), independent of clinical response (Group x Session $F=0.51$). HADS Anxiety disclosed a tendency towards a reduction ($F=3.39$, $df=1,15$, $p<0.086$), also independent of clinical response (Group x Session $F=0.16$). Furthermore changes in anxiety and depression were unrelated to the number of practice sessions ($r<0.215$). Participation in the study had a beneficial effect on both anxiety and depression, whether or not there was clinical improvement; however, relief from anxiety was associated with clinical benefits. Correlational analysis confirmed a significant positive correlation between reduced frequency of recurrence and reduced HADS Anxiety ($r=0.591$, $p=0.016$).

There were no differences between responders and non-responders on the mood activation checklists ($F<2.95$), nor were there significant correlations between mood and the change in occurrence ($r<0.286$). There was a tendency for practice to be associated with an increase in calmness ($r=0.452$, $p=0.059$), but no significant associations with changes in tension, energy or lethargy ($r<0.341$).

Personality scales

Relations between the EPQ and the PSQ Activated subscales were complex. Strong positive relations were found with Extraversion and PSQ subscales of Behavioural Activity ($r=0.641$, $p=0.002$) and Activated Speech ($r=0.656$, $p=0.002$). However, there was a negative correlation between Extraversion and Odd Behaviour ($r=-0.441$, $p=0.045$). The latter in turn correlated positively with Psychoticism ($r=0.573$, $p=0.008$), while Odd Speech correlated positively with Neuroticism ($r=0.485$, $p=0.03$).

In contrast relations between PSQ Withdrawal and EPQ Introversion and Neuroticism were straight forward, and EPQ Neuroticism correlated in the traditional way with EPQ Introversion ($r=0.461$, $p=0.041$). The Withdrawn syndrome showed moderate to high correlations with Introversion: Withdrawn total ($r=0.704$, $p=0.0001$), Withdrawn Behaviour ($r=0.777$, $p=0.0001$), Constricted Affect ($r=0.586$, $p=0.007$) and Social Anxiety ($r=0.704$, $p=0.001$). In addition, the Withdrawn syndrome showed moderate correlations with Neuroticism: Withdrawn Total ($r=0.522$, $p=0.018$) and Social Anxiety ($r=0.578$, $p=0.008$). The Withdrawn syndrome also correlated positively with the Lie Scale: Withdrawn total ($r=0.539$, $p=0.014$), Withdrawn Behaviour ($r=0.548$, $p=0.012$) and Social Anxiety ($r=0.452$, $p=0.045$).

There were also congruent relations between the personality scales and mood. Activation correlated positively with Energy both at baseline ($r=0.603$, $p<0.006$) and following hypnosis ($r=0.490$, $p=0.028$). The Withdrawn syndrome correlated with HADS Depression at baseline: Withdrawn Total ($r=0.469$, $p=0.031$); Constricted Affect ($r=0.604$, $p=0.005$), Social Anxiety ($r=0.469$, $p=0.037$), and Depression correlated with Constricted Affect following hypnosis ($r=0.563$, $p=0.012$). Both HADS Anxiety and Depression at baseline correlated with Introversion ($r=0.408$, $p=0.074$; $r = 0.485$, $p=0.03$).

Personality and clinical response

Germane to predictions Cognitive Activation correlated with the number of HSV-2 episodes during the six weeks of hypnosis training. The higher the Cognitive Activation the fewer were the episodes of herpes ($r=-0.515$, $p=0.02$). This was also found to a lesser extent with the Activation total score ($r=-0.426$, $p=0.06$).

This relation could be interpreted as a demonstration that cognitive activation predicted a better clinical response to hypnotherapy independent of motivation and other extraneous factors for there was no correlation between personality and frequency of tape use ($r_s<0.09$), and because *t*-test differences between responders and non-responders were non-significant. No other personality scale, notably Withdrawal, was associated with the number of episodes or clinical response to hypnotherapy

Personality and immunity: Cognitive Activation

In keeping with the associations between Cognitive Activation and clinical response, Cognitive Activation correlated positively with the degree of increase in Natural Killer cell parameters; examples are shown in Figure 1. This was seen with NKC cytotoxicity, including: the increase following hypnotherapy in HSV specific cytotoxicity ($r = -0.753$, $p=0.051$; Figure 1(a)), the change in HSV specific LAK activity ($r=-0.886$, $p=0.008$; Figure 1(b)) and seen in the positive correlation with post-hypnosis levels of HSV specific cytotoxicity ($r=0.804$, $p=0.029$). A correlation with HSV specific ADCC activity approached significance ($r=0.582$, $p=0.078$).

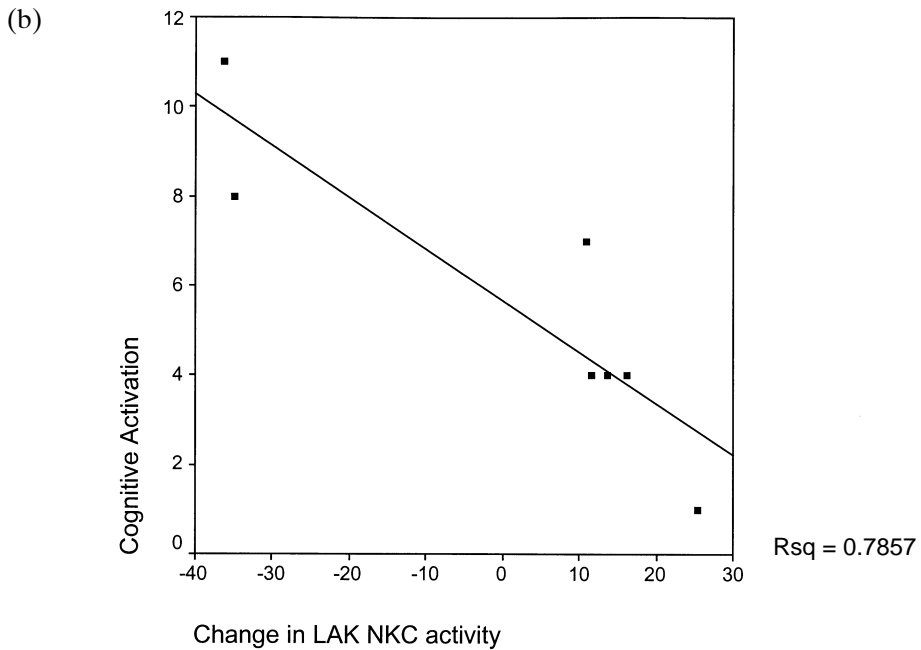
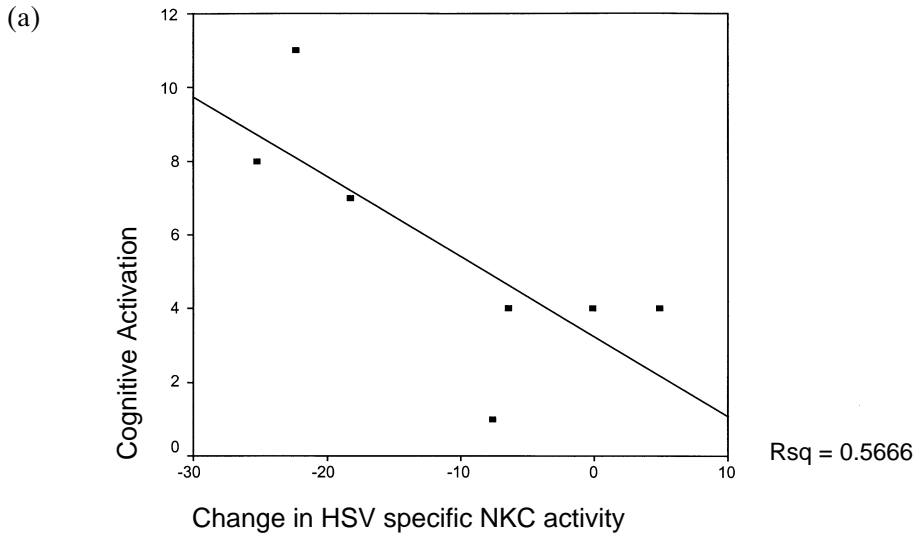


Figure 1: Scatterplots of the correlations between: (a) cognitive activation and the increase in HSV specific cytotoxicity; (b) cognitive activation and the change in HSV specific LAK activity; (c) cognitive activation and baseline HSV specific cytotoxicity; (d) withdrawn affect and NKC number at baseline.

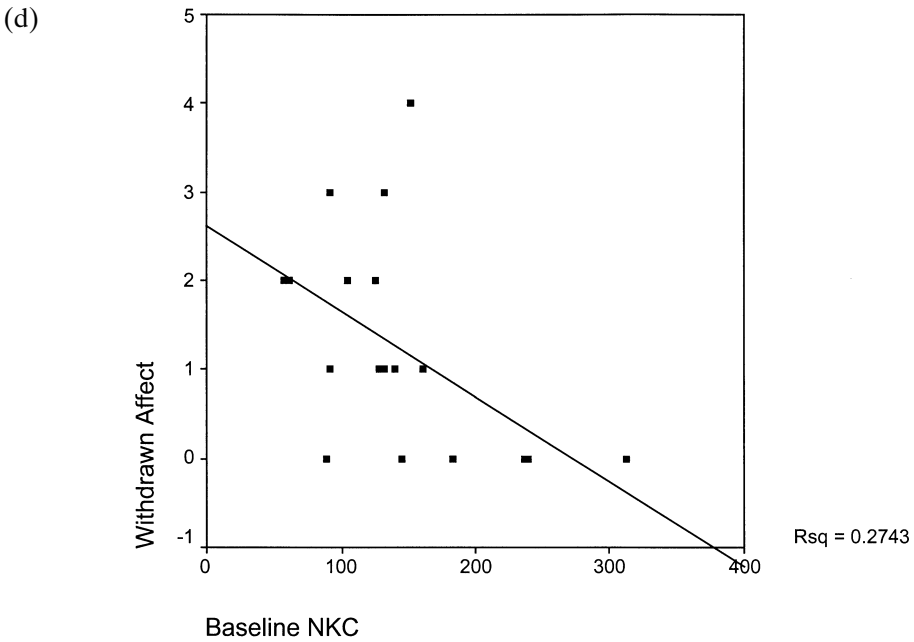
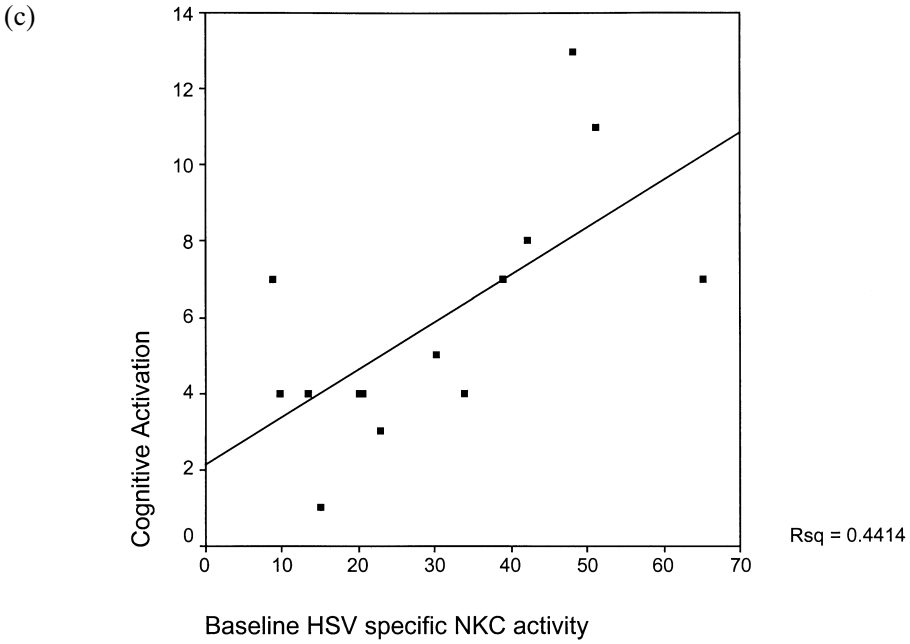


Figure 1: (Continued)

Cognitive Activation also correlated positively with baseline levels of HSV specific cytotoxicity ($r=0.664, p<0.01$; Figure 1(c)), HSV specific LAK activity ($r=0.599, p=0.018$), while the correlation with NKC numbers was in the same direction ($r=0.48, p=0.097$).

Regarding other lymphocytes the Activation subscale Odd Behaviour correlated in the direction of high scores and a decrease in lymphocytes, that is in the opposite direction to the positive relation between up-regulation and Cognitive Activation: CD3+ ($r=-0.552, p=0.022$), CD4+ ($r=-0.553, p=0.021$), CD8+ ($r=-0.437, p=0.079$) and CD19+ ($r=-0.594, p=0.012$).

Personality and immunity: Withdrawal

The Withdrawn syndrome correlated negatively with NKC activity; that is, the opposite polarity to Cognitive Activation. These relations were only found at baseline. Consideration of Withdrawn subscales indicated that significant results or tendencies related to the affective as distinct from behavioural aspects of withdrawal: Withdrawn Total (NKC%, $r=-0.519, p=0.039$; NKC number, $r=-0.541, p=0.032$; HSV specific ADCC activity, $r=-0.593, p=0.052$); Withdrawn Affect (NKC%, $r=-0.517, p=0.04$; NKC number, $r=-0.630, p=0.003$, Figure 1(d); HSV specific ADCC activity, $r=-0.528, p=0.115$); Social Anxiety (NKC%, $r=-0.462, p=0.055$; NKC number, $r=-0.440, p=0.068$; HSV specific ADCC activity, $r=-0.656, p=0.026$).

Neuroticism was also associated with NKC activity at baseline: non-specific activity ($r=-0.586, p<0.02$); LAK ($r=-0.617, p<0.029$); ADCC activity ($r=-0.798, p=0.005$). None of the other EPQ scales such as Extraversion-Introversion, Psychoticism or the Lie scale correlated with the immune variables.

Affect and immunity

Consistent with positive correlations between Withdrawal and the HADS scales of Depression and Anxiety, the latter were also associated with immunosuppression, but these relations were with lymphocyte counts (CD3+, CD4+, CD8+, CD19+) and cortisol, particularly in the post-hypnosis assay. The relations were more consistent with Depression than with Anxiety: CD3+ (Depression, $r=-0.599, p=0.009$; Anxiety, $r=-0.547, p=0.019$); CD4+ (Depression, $r=-0.587, p=0.01$; Anxiety, $r=-0.506, p=0.032$); CD8+ (Depression, $r=-0.423, p=0.08$; Anxiety, $r=-0.434, p=0.072$); CD19+ (Depression, $r=-0.503, p=0.033$; Anxiety $r=-0.330$, ns); cortisol (Depression, $r=-0.575, p=0.01$; Anxiety, $r=-0.298$, ns). The Thayer scales were not associated with immune function.

Hypnotizability

As there was only a moderate correlation between the objective and subjective measures of hypnotic suggestibility ($r=0.554, p=0.011$), as found previously (Williams, Croft and Gruzelier, 1999) correlations were examined with the subscales in addition to the combined score.

Hypnotizability and immunity

On several counts hypnotizability (Total, Objective and Subjective) correlated positively with immune system up-regulation with respect to specific and non-specific measures: increase in NKC% ($r=0.535, p=0.049$), increase in HSV-2 specific LAK ($r=0.975, p=0.025$) and post-hypnosis CD8 counts ($r=0.507, p=0.027$). These were largely due to the Objective subscale: increase in NKC% ($r=0.541, p=0.033$), increase in CD8+ counts ($r=0.562, p=0.019$) and post-hypnosis counts ($r=0.517, p=0.023$). In contrast the Subjective subscale correlated positively with baseline lymphocyte counts: CD3+ ($r=0.611, p=0.007$), CD4+ ($r=0.473, p=0.048$) and CD8+ ($r=0.535, p=0.022$).

Hypnotizability and affect

Hypnotizability total score was associated with an improvement in depression, as shown by a positive correlation with the reduction in HADS Depression ($r = 0.46, p < 0.048$) and a negative correlation with the post-hypnosis rating of Depression ($r = -0.477, p < 0.039$). The Subjective subscale was positively correlated with the reduction in Thayer Tiredness ($r = 0.534, p = 0.019$).

In later investigations hypnotizability was found positively correlated with PSQ Unreality, a subscale not included here (Jamieson and Gruzelier, 2001; Gruzelier, 2002c).

Hypnotizability and personality

In keeping with previous research, hypnotizability was not correlated significantly with the EPQ or with PSQ Activation and Withdrawal ($r = 0.320$ to -0.271). The Objective hypnotizability subscale correlated positively with practice ($r = 0.462, p < 0.046$), whereas there was no relation with the Subjective scale ($r = 0.098$).

Discussion

The main findings of the study were as follows:

- 1 Participation in the study substantively reduced the rate of recurrence of HSV-2 in 65% of patients who had severe, chronic illnesses.
- 2 Clinical improvement was accompanied by up-regulation of immune parameters specific to the illness such as NKC for HSV, as well as non-specific parameters such as NKC counts.
- 3 While frequency of practice did not relate to herpes outcome, it was positively associated with up-regulation in some specific and non-specific parameters, but was unrelated to reductions in depression and anxiety.
- 4 Participation in the study in itself was sufficient to produce benefits in both responders and non-responders in T-lymphocytes and clinical anxiety and depression.
- 5 The activated personality, particularly cognitive activation, was positively associated with reduced herpes recurrence, improvements in specific NKC cytotoxicity, baseline functional NKC activity and energy ratings, and was unrelated to frequency of practice.
- 6 Withdrawal, particularly the affective aspects, and Neuroticism were negatively associated with NKC counts and NKC functional activity at baseline, independent of herpes recurrence rate, and positively associated with depression and/or anxiety at baseline.
- 7 Clinical Depression, and to a lesser extent Anxiety, was negatively associated with lymphocyte counts at baseline.
- 8 Hypnotizability was associated positively with aspects of immune system up-regulation, such that the objective scale was positively associated with up-regulation of specific and non-specific immune parameters, while the subjective scale was associated with baseline lymphocytes.
- 9 Hypnotizability was negatively associated with clinical depression and the subjective subscale positively with the reduction in tiredness following hypnotherapy.

There have been many reports of changes in immunity following psychological interventions, which have been interpreted as beneficial in their effects (for review see Gruzelier, 2002a, 2002b). These have included interventions with healthy subjects and with

patients with single procedures such as progressive muscle relaxation, mental relaxation, meditative music relaxation and improvisation, autonomic biofeedback, flotation with restricted environmental stimulation, as well as hypnosis. Increasingly mixed intervention approaches have been adopted, most commonly combining various forms of relaxation and imagery training with autonomic biofeedback, often with additional cognitive and social approaches. However, although these have been often accompanied by improvements in mood, the significance of the alterations in immunity have been unclear. This is because of the complexity of brain-immune interactions in what is a dynamic, highly redundant system full of checks and balances, redistribution and migration (Evans et al., 2000; Ader et al., 2001). Accordingly, if psychological interventions are to win acceptance, evidence is required for improvements in health and alterations in immune parameters salient to the disease process.

Though small in scale these studies of hypnotic imagery training in preventing illness at exam time in medical students (Gruzelier et al., 2001b) and reducing recurrence of herpes in patients with chronic infection (Fox et al., 1999) represent a small step in providing evidence of benefits for health. Fewer students who trained with hypnotic imagery of the immune system fell ill with winter viruses than those trained with relaxation imagery or who participated as non-intervention controls, and this was accompanied by non-specific immune system up-regulation and improvements in well-being. In patients with a chronic and virulent viral illness there was a 48% reduction in recurrences of the herpes infection, and in the year following the study some patients remained off medication and experienced very little recurrence of HSV-2. Of added importance was the disclosure of the disease relevance of the immune changes taking the form of improved natural killer cell cytotoxicity for the herpes virus (HSV-1), as well as HSV specific cytotoxicity following stimulation with interleukin-2, also accompanied by non-specific immune system up-regulation and improvements in well-being. These results may help win acceptance for the application of hypnotherapy for viral illness prevention and treatment.

Independent of the viral outcome, hypnotherapy had beneficial influences on pathological depression in clinical responders and non-responders and to a lesser extent on anxiety and up-regulation of T-lymphocytes. Hypnotizability was also positively correlated with reductions in depression and tiredness, while the more hypnotizable subjects showed lower levels of depression following hypnotherapy. Hypnotizability also correlated positively with up-regulation of some specific and non-specific NKC activity measures and CD8+ lymphocytes, more so in respect of the Objective subscale. The Subjective subscale correlated positively with CD3+, as well as CD4+ and CD8+ lymphocyte counts. Differential associations with immunity and objective versus subjective hypnotizability scales support the complex nature of hypnotic responding. There was also evidence that the greater the frequency of practice of self-hypnosis the greater was the immune enhancement with respect to specific NKC cytotoxicity indicators and non-specific numerative measures of NKC and CD8+ helper lymphocytes. At the same time improvements in health were not restricted to those who practised frequently, and in students improvements in health and up-regulation of immunity were not always associated with hypnotic susceptibility (Gruzelier et al., 2001a).

Regarding the main focus of this report, namely the replication of the role of the personality measure, cognitive activation, in predicting improvements in health and in specific immunity, the results were affirmative. Cognitive activation predicted herpes recurrence such that the greater the activation the better the response to hypnotherapy.

Cognitive activation also predicted the functional enhancements in a range of virus specific NKC parameters including cytotoxicity in response to HSV-1 and the response to stimulation by interleukin-2, as well as post-hypnosis training cytotoxicity levels. Cognitive activation also predicted baseline NKC cytotoxicity. Thus cognitive activation manifested important predictive properties with regard to specific immune changes of relevance to the virus encompassing parameters at baseline and following self-hypnosis training, as well as the degree of up-regulation as a result of hypnotherapy.

In the original student study (Gruzelier et al., 2001a), while there was no relation with NK cell counts, cognitive activation correlated positively with the full range of T- and B-lymphocytes. Cognitive activation predicted both the increase in lymphocyte numbers in the course of the study, as well as the levels sustained at the end of study during the exam period. In fact the degree of maintenance of lymphocyte counts in the face of exam stress that was predicted by personality occurred independently of the benefits of hypnosis, and indeed was seen more strongly in the control group. In other words, self-hypnosis was beneficial over and above the personality difference, helping to buffer the influence of stress on lymphocytes irrespective of a natural advantage associated with a cognitively activated personality.

The patient and student studies were distinguished by the fact that in students the relation with cognitive activation was seen with lymphocytes and not with natural killer cells, whereas in patients it was the reverse. The absence of influence on natural killer cells in students may be due to several issues. No functional NKC measure as distinct from numerative measures (counts of NKC) was obtained in students. The more expensive to assay, functional measures are more informative than numerative measures, particularly when they demonstrate specificity for the virus under study. In addition, as discussed elsewhere (Gruzelier, 2002a), longitudinal monitoring of NKC counts in students, along with lymphocytes, has disclosed that manifold stressors operate on students throughout the academic year. These stressors vary *inter alia* with students' familiarization with university life, with the result that they may mask the influences of psychological interventions (Whitehouse et al., 1996; Gruzelier, 2000a).

Another distinguishing factor was the correlation in the clinical study between baseline immune parameters and personality. Not only were these in the form of positive correlations with cognitive activation, but they extended to negative correlations with Withdrawal, especially its affective component, along with EPQ Neuroticism and HADS Clinical Depression and Anxiety scales. Negative correlations between immune parameters and negative affect are consistent with the original pioneering findings of the link between psychological factors and immunity. The absence of the relation between withdrawal and immunity in the students is a likely outcome of the low levels of withdrawal in the medical students volunteering for the study, in contrast to the patients who had high levels of anxiety and depression.

The 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 regarding immune system up-regulation. They are complementary with respect to both positive personality influences on immunity and the negative influences of depressive affect, stress and anxiety, through the bipolarity of activation-withdrawal. It is noteworthy that while there was a commonality across the PSQ, EPQ and HADS measures of negative affect and withdrawal, there were no parallels between Cognitive Activation and the other personality scales such as Extraversion, Psychoticism and the Lie Scale. These EPQ scales did not correlate with immunity or health. The opposite correlations of the Odd Behaviour activation subscale

with immune parameters from the other activation scales may reflect personality features particular to the patient sample with their compromised social behaviour as a result of the severe and chronic virus. The fact that Odd Behaviour was the only measure to correlate with Psychoticism may also attest to the interpretation.

Insights are also offered about neurophysiological underpinnings. The construct of the activated personality first grew out of research on functional laterality and schizophrenia (see Gruzelier, 1999 for review). Activated versus withdrawn syndromes were originally delineated by psychophysiological asymmetry parameters and subsequently were found to be characterized by a range of lateralized neuropsychological and psychophysiological processes in schizophrenia. Subsequently these syndromes were found to apply to personality dimensions in the normal population, where they were also associated with opposite cognitive functional asymmetry patterns.

The applicability of functional laterality to immune function follows evidence of lateralized influences on the immune system, notably in animals (see Neveu, 2002 for review). In humans, reduced NK cell activity has been found in nurses with a preferential right frontal EEG activation compared with those with the opposite asymmetry (Kang, Davidson, Coe, Wheeler, Tomarken and Ershler, 1991). Clow, Lambert, Evans, Hucklebridge and Higuchi (2002) have reported theoretically consistent asymmetries in salivary IgA and free cortisol concentration following lateralized trans-magnetic stimulation of temporo-parietal occipital cortex. One controversial model has linked an increased incidence of immune disorders with left handers, who though heterogeneous, as a group have a greater reliance on right hemispheric processing (Geschwind and Behan, 1984; Geschwind and Galaburda, 1985). Another model has incorporated evidence of lateralized influences on the immune system from animal studies with hemispheric specialization theory, including associations between the left hemisphere and approach behaviour, positive affect and immune system up-regulation, and associations between the right hemisphere and withdrawal, negative affect and immune down-regulation (Gruzelier, 1989). In support of the model, both EEG and neuropsychological asymmetry patterns in asymptomatic men with HIV infection 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 (Gruzelier, Burgess, Baldeweg, Riccio, Hawkins, Stygall, Catt, Irving and Catalan, 1996).

In sum the cognitively activated temperament versus the withdrawn temperament may be aligned with left and right hemispheric specializations in the form of approach (left) versus avoidant (right) behaviour (and hence the chosen descriptors activated and withdrawn), as well as with hemispheric specializations that relate to positive (left) versus negative (right) affect. The particular relation here between immune function and cognitive activation, which includes speaking and thinking quickly, provides compelling support for the association of immune system up-regulation with left hemisphere functional preference, given the unambiguous left hemisphere involvement in speech production. There are also clear links between the activated personality dimension and the fighting spirit, laughter and exercise, which have demonstrable advantages for immune function (Greer, 1983; Valdimarsdottir and Bovbjerg, 1997; Fernandez-Ballesteros et al., 1998; Skevington and White, 1998).

Finally, the activated versus withdrawn personality dimensions, aside from providing insights into the neurophysiological basis of mechanisms mediating psychoneuroimmunological influences, have value for therapy. 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, generative, cognitive requirement appears to be the more successful form of intervention than the more passive imagery of relaxation training (Gruzelier et al., 2001b). The patients with severe and chronic genital herpes proved to be an insightful group for studying the effects of personality and hypnotherapy. The study has replicated the advantages of an activated personality for immune functioning at baseline and for both immune functioning and health in response to the psychological intervention. It has also demonstrated the benefits of hypnotherapy for a chronic viral illness and for the up-regulation of immune parameters with specificity for the herpes virus as well as non-specific immunity.

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