

## Hypnosis from a neurobiological perspective: A review of evidence and applications to improve immune function \*

John Gruzelier\*\*

*Imperial College of Science, Technology & Medicine, London*

**Título:** La hipnosis desde una perspectiva neurobiológica: Una revisión de la evidencia y aplicaciones a la mejora de la función inmune.

**Resumen:** Se revisa la evidencia neuropsicofisiológica que sirve de prueba a un modelo de trabajo, en tres etapas, de la inducción hipnótica tradicional por relajación, y que incluye: 1) una red atencional talamocortical que implica al sistema frontolímico de control de la atención focalizada del hemisferio izquierdo que sostiene la fijación sensorial y la concentración en la inducción; 2) toma del control por parte de los sistemas inhibitorios frontolímicos, mediante las sugerencias de cansancio y relajación, con lo que las funciones ejecutivas anteriores quedan en suspenso y pasan a ser dirigidas por la inducción; 3) implicación de las funciones temporoposteriores propias del hemisferio derecho a través de la imaginación pasiva y el sueño. Una marca característica de los estudios fue la selectividad de acción en los sujetos muy susceptibles. Un incremento en la interferencia Stroop coincidió con el mantenimiento de la detección de errores y la supresión de los potenciales de evaluación del error, lo que se interpreta como una disociación de los sistemas ejecutivos afectivo y cognitivo del cíngulo anterior. Se observó una disociación entre las tareas de fluidez verbal, categórica y de diseños, con un efecto específico de la hipnosis sobre los procesos propios de la región anterior izquierda, reflejado también en la reducción, medida con EEG, de la conectividad entre la zonas medial y lateral izquierda. Se inhibieron las respuestas electrodérmicas de orientación, moduladas por el sistema límbico, y la Mismatch Negativity (MMN) modulada por la región frontal. Las asimetrías en las respuestas electrodérmicas y electrocorticales a los tonos cambiaron a favor del hemisferio derecho, asimetría también observada en la sensibilidad visual. El procesamiento háptico y la sensibilidad visual revelaron cambios más distribuidos en los sujetos con un nivel medio de susceptibilidad, mientras que los no susceptibles se caracterizaron por unas funciones atencionales más pobres en la línea base, que mejoraron con la inducción.

**Palabras clave:** Neurofisiología de la hipnosis, respuesta inmune.

**Abstract:** Neuropsychophysiological evidence is reviewed testing a three-stage, top down working model of the traditional hypnotic relaxation induction involving: 1) a thalamocortical attentional network engaging a left frontolimbic focussed attention control system underpinning sensory fixation and concentration on the induction; 2) instatement of frontolimbic inhibitory systems through suggestions of tiredness at fixation and relaxation whereby anterior executive functions are suspended and directed by the induction; 3) engagement of right-sided temporoposterior functions through passive imagery and dreaming. A selectivity of action in high susceptibles was a hallmark of the studies. Increased Stroop interference coincided with maintenance of error detection and abolition of error evaluation potentials, interpreted as dissociation of cognitive and affective executive systems of the anterior cingulate. Verbal, category and design fluency tasks were dissociated with hypnosis centring on left anterior processes as seen in left lateral and medial reduced EEG connectivity. Limbic modulated electrodermal orienting responses and frontal modulated mismatch negativity waves were inhibited. Asymmetries in electrodermal and electrocortical responses to tones shifted to favour the right hemisphere, an asymmetry also seen in visual sensitivity. Haptic processing and visual sensitivity disclosed more distributed changes in medium susceptibles, while low susceptibles were characterised by poorer attentional functions at baseline and improvements through the induction.

**Key words:** Neurophysiology of hypnosis, immune response

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\*\* **Dirección para correspondencia / Address for correspondence:** Professor John Gruzelier, Department of Behavioural & Cognitive Sciences, Imperial College School of Medicine, St Dunstons Road, London W6 8RF.  
E-mail: j.gruzelier@ic.ac.uk

## Introduction

This article provides a review of experiments, thematically rather than chronologically structured, carried out in the Charing Cross laboratory of Cognitive Neuroscience with the aim of understanding the neuro-psychophysiological basis of hypnosis and applying self hypnosis to improve immune function. Hypnosis was defined operationally on the basis of the traditional relaxation procedure which began with eye fixation, suggestions of relaxation and eye closure, and was followed by imagery associated with deep relaxation and a dream. This was applied in all experiments except one where the active-alert procedure (Banyai & Hilgard, 1976) was compared. Regarding self hypnosis the induction was supplemented by guided imagery relating to immune function and positive mood and esteem. The induction was typically presented with a tape recorder. In the laboratory, during the induction there were behavioural challenges to assess depth of hypnosis, and at the end questions about memory for the induction, a post hypnotic suggestion and subjective ratings. This is an important innovation to test the reliability of initial screening procedures and to validate the susceptibility classification. The purpose of the studies was to unravel some of the changes in brain activity that accompany the hypnotic induction in both high and low susceptible individuals, and features that may differentiate them in the baseline state. Applications of self hypnosis to improving health were also explored.

The history of localising neurophysiological mechanisms in hypnosis began by likening hypnosis to sleep. Pavlov demonstrated the existence of hypnosis in his conditioned reflex studies in dogs and attributed this to a partial and spreading inhibition of the cortex, less extensive than occurs in sleep, though Heidenhain had reasoned earlier that more than the cortex was involved because animals did not behave as if they were decorticate (Windholz,

1996). Though sleep became an increasingly popular analogy, to date electroencephalographic (EEG) studies have not found similarities between hypnosis and sleep (for a review see Crawford and Gruzelier, 1992). At the same time sleep can be induced by instructions of hypnosis, but conventional procedures stop short of sleep induction. Hernandez-Peon (1977) proposed that hypnosis was closer to wakefulness than sleep, involving alterations in both consciousness and executive functions which he localised to the midbrain, pons and medulla. Nevertheless, depending on the nature of the induction, dream-like features are close to the hypnotic experience of many high susceptibles.

Recordings from intracranial electrodes in epileptic patients have disclosed the importance of limbic structures in hypnosis. Crasileck, McCranie & Jenkins (1956) reported anecdotally that hypnosis was terminated each time the hippocampus was electrically stimulated. With more modern procedures De Benedittis and Sironi (1986) demonstrated in a high hypnotisable that there was a reduction in interictal focal abnormalities in the hippocampus during hypnosis and an increase in alpha activity. In a second patient they concluded that hypnosis was associated with functional inhibition of the amygdala, because stimulation of the amygdala aroused the patient from hypnosis unlike stimulation of the adjacent and reciprocally connected hippocampus. Electrical activity in the amygdala became synchronised with hypnosis whereas activity in the hippocampus became desynchronised (De Benedittis & Sironi, 1988).

In the 1960s parallels were drawn between hypnosis and right hemispheric processing and high hypnotic susceptibles were assumed to be characterised by right hemisphericity. This point of view has been popularised and has been found to be important in the clinical use of hypnosis (Pedersen, 1984). Aside from evidence from cognitive studies with putative

hemisphere specific tasks, there were also neuropsychophysiological measures which took into account brain anatomy such as EEG, dichotic listening and conjugate lateral eye movements (Crawford and Gruzelier, 1992). Experimental evidence was, however, conflictual, but the methodology of many studies were questionable (Gruzelier, 1988). Methods of inducing hypnosis were various and often poorly described. Often there was a failure to distinguish between high and low susceptibles or to attribute changes in low susceptibles that were absent in high susceptibles to the hypnotic process. Seldom was evidence cited of test-retest reliability, or of replication, or of validation of hypnotic level during the experimental procedure.

In integrating the results of a decade ago a three stage working model of the induction process was proposed (Gruzelier, 1988, 1990). Stage I: The initial instructions of fixating on a small object and listening to the hypnotist's voice was posited to involve an attentional network including thalamocortical systems and parietofrontal connections with engagement of a left anterior focussed attention control system. This underpins the focussed, selective attention inherent in fixation and listening to the hypnotist's voice, processes which together require left hemispheric frontotemporal processing. Stage II: This first stage is then replaced by eye closure, suggestions of fatigue at continued fixation, and tiredness together with deep relaxation. This sets in motion frontolimbic inhibitory processes underpinning the suspension of reality testing and critical evaluation, and the handing over of executive and planning functions to the hypnotist; the "letting go" component of the hypnotic induction. Stage III: The third stage involves instructions of relaxed, passive imagery leading to a redistribution of functional activity and an augmentation of posterior cortical activity, particularly of the right hemisphere in high susceptibles. Simplifying the verbal content of the induction

message may also facilitate right hemispheric processing as does emphasising past experience and emotion. In contrast the low susceptible fails to show engagement of left frontal attentional control mechanisms, or if there is focal attentional engagement the low susceptible fails to undergo the inhibitory, letting go process. This working model will serve to structure the review of findings.

### **Thalamo-frontal-limbic attentional processes.**

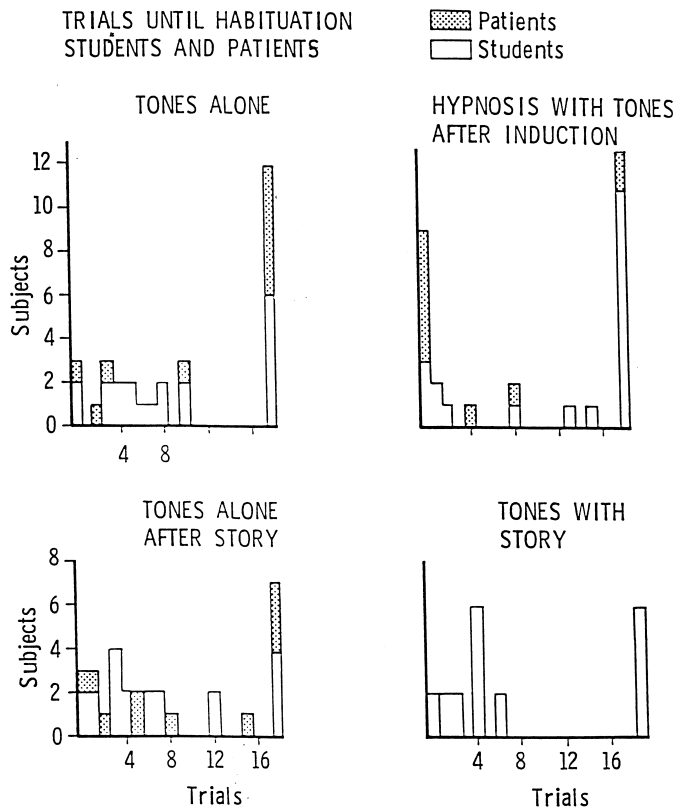
#### **Electrodermal Orienting, Habituation, Sensitisation and Tonic Reactivity.**

We first investigated the basic attentional processes of orienting, which represents focussing of attention, and of habituation with stimulus repetition, which allows attention to be redirected, and which together involve modulation by the limbic system, in particular the amygdala and hippocampus (e.g., Pribram and McGuinness, 1975; Gray, 1982). The electrodermal response was chosen because among physiological measures it has the advantage of indexing sympathetic nervous system activity unconfounded by competing parasympathetic influences. Using a standardised tone orienting and habituation paradigm (Gruzelier and Venables, 1972) we monitored in normal and patient volunteers the effects of hypnosis on orienting responses to tones that were interspersed with the hypnotic induction (Gruzelier and Brow, 1985). Subjects took part in three sessions separated by four weeks to avoid carryover effects on habituation. They were first monitored to provide a baseline measure and to equate groups for individual differences in rate of habituation. Then with session order counterbalanced they experienced a hypnosis session and one of two control conditions. The control conditions consisted of either a story read by the hypnotist, or relaxing listening to a story for a period

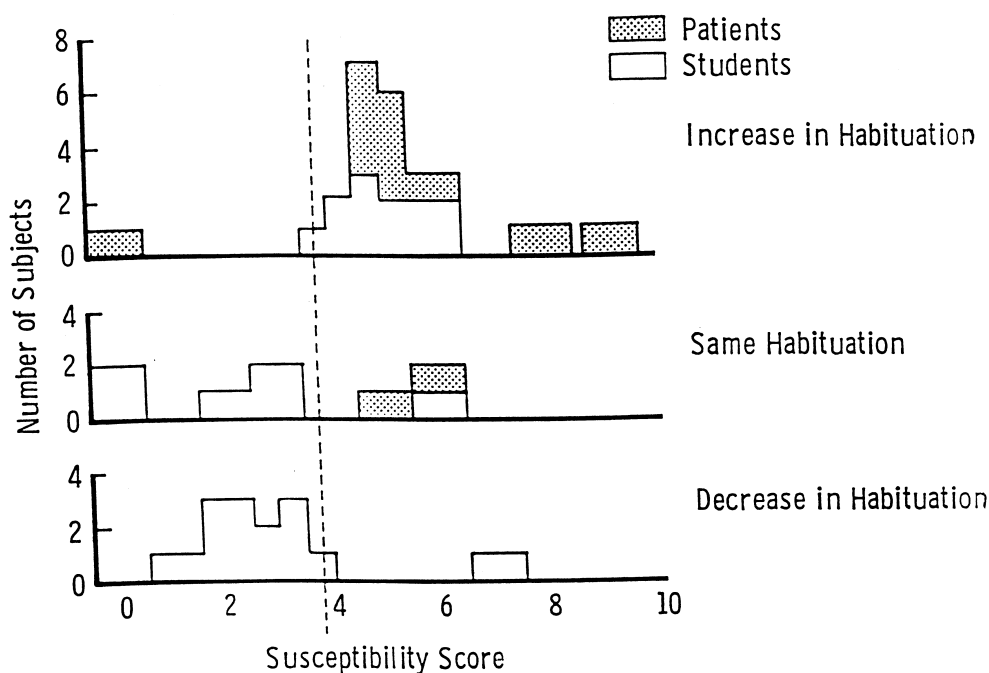
equivalent in length to the hypnotic induction prior to the introduction of the tones which were presented without any accompanying verbal message. Hypnotic susceptibility was monitored throughout the experimental session

The outcome was clear and depended on level of susceptibility. As shown in Figure 1, in the group distributions of orienting and rate of

habituation, the hypnosis condition was distinguished from the three control conditions through a higher incidence of both nonresponding and non-habituation, a bimodal distribution. It was the high susceptibles who showed a reduction in orienting and/or faster habituation with hypnosis, whereas low susceptibles showed retarded habituation with hypnosis, as can be seen in Figure 2.



**Figure 1:** Electrodermal orienting response habituation in baseline (tones alone), hypnosis, relaxation after listening to a story, and story conditions.



**Figure 2:** Subjects categorised according to increase, decrease or no change in habituation from baseline to hypnosis as a function of induction susceptibility score.

Comparisons with other features of electrodermal activity shed light on arousal and attentional processes. For the group as a whole, in hypnosis there was an absence of sensitisation to a test tone presented towards the end of the session while throughout the induction there was an increase in electrodermal non-specific responses. It is important to note that both these effects were shared with the control story condition and did not vary with hypnotic susceptibility. From this we can infer that listening to the story and to the hypnotic induction produced a similar degree of autonomic arousability and attentional engagement and these did not vary with susceptibility. Turning to the relaxation condition, this was insufficient to change either habituation (see also Teasdale, 1972) or sensitisation, so that the facilitation of habituation could not be explained away as a function of relaxation.

At the same time some components of arousal reduction were associated with hypnosis. This was shown by fewer non-specific responses during hypnosis both in the first half and second half of the hypnotic induction as well as by reductions in tonic levels of skin conductance. However, one high susceptible had levels of skin conductance two standard deviations above the control group mean, indicating that a reduction in tonic arousal is not a necessary part of the hypnotic process as will be confirmed later in an experiment with the active-alert induction procedure.

The facilitation of habituation with hypnosis was replicated in an experiment designed to compare hypnosis with *simulating hypnosis* in medium/high hypnotisables (Gruzelier, Allison & Conway, 1988). Subjects were examined first in a baseline session and then assigned on the basis of the Barber Suggestibility Scale

(Barber, 1969) to the simulator or hypnosis groups matched for electrodermal reactivity, sex and suggestibility. Hypnotic susceptibility was monitored throughout the second session as in the former experiment. Levels of susceptibility all fell within the moderate to high range. As before rate of habituation was faster with hypnosis in the susceptible subjects while in simulators habituation was slower. Simulators were more aroused during the induction prior to presentation of the tones ( $p < 0.005$ ) but subsequently there was no difference in the number of nonspecific electrodermal responses. Support was found for reports that simulators are characterised by exaggerated compliance (Williamsen, Johnson & Eriksen, 1965; Hilgard, McDonald, Morgan & Johnson, 1978), for in compliance with instruction by the hypnotist to forget about the tones, all but one simulating subject claimed at the end of the session not to have heard the tones, whereas all but one in the hypnosis group admitted to hearing the tones.

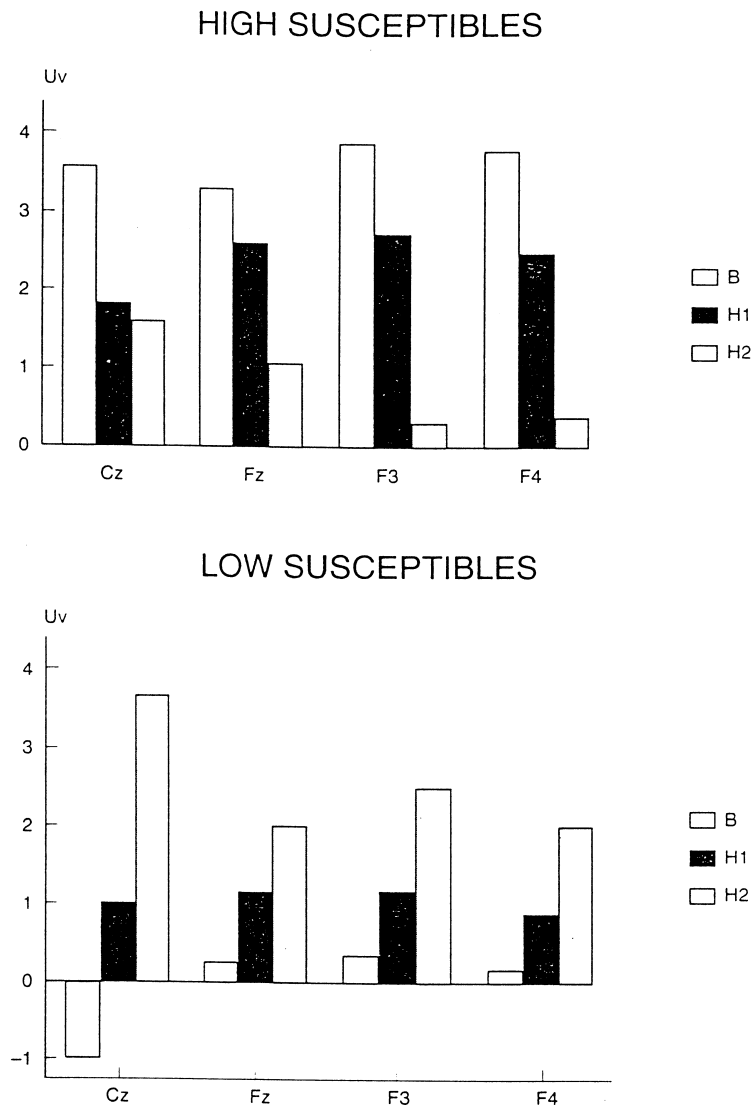
Neuroanatomically the influence on electrodermal orienting and habituation was compatible with the evidence of De Benedittis and Sironi (1988) arising from recordings of intracranial electrical activity. They found that hypnosis involved functional inhibition of the amygdala and activation of the hippocampus. The amygdala has been shown to exert mainly excitatory influences on orienting activity whereas the inhibitory action of the hippocampus facilitates the habituation of the orienting response with stimulus repetition (Gruzelier & Venables, 1972; Pribram & McGuinness, 1975).

#### **Electrocortical Event-Related Attentional Components and Frontal Inhibition.**

Electrocortical procedures have also demonstrated alterations in attentional processing with the induction of hypnosis, and like electrodermal rates of habituation these chan-

ged in opposite directions from baseline to hypnosis for high and low susceptibles (Gruzelier, 1996). Cortical evoked potentials were measured to infrequent tones mixed with frequent tones in a standard P300 paradigm with particular interest in a negative going (N2a) attentional component. The difference between the wave to the infrequent target or deviant when subtracted from the frequent non-target or standard belongs to the class of phenomena termed MisMatch Negativity (MMN). This is thought to involve a preattentive sensory specific process generated in auditory cortex (superior temporal gyrus). Aside from bilateral temporal maxima it has a predominant single maximum over the frontal cortex suggestive of frontal involvement (Näätänen, 1992).

Before the topographical EEG recording session subjects were assigned with the Harvard Group scale (Shor and Orne, 1962) to high (9-12) and low (0-4) susceptibility groups. Baseline measures were first recorded and these were repeated following the hypnotic induction as in the electrodermal studies, and repeated a second time following an extended induction. Susceptibility was recorded throughout the session as in previous studies. As can be seen in Figure 3 high susceptibles showed a large magnitude difference wave at baseline and a progressive reduction in MMN with each stage of the induction and in keeping with frontal inhibition. By the later stage of the induction MMN was negligible in both the lateral frontal placements. Importantly opposite changes were manifested by the low susceptible group. Whereas at baseline their difference wave was absent, there was a progressive increase in MMN through the experiment, until in the last condition the magnitude of the difference wave was on a par with the results in high susceptibles at baseline, suggesting an increasing enhancement of attentional processing.



**Figure 3.** Nd wave scores in baseline (B), induction (H1) and extended induction (H2) in high and low susceptible groups.

**Summary**

There was a consistency between the electrocortical MMN and electrodermal measures in depicting opposite changes from baseline to hypnosis in susceptible and unsusceptible sub-

jects. Congruent opposing effects on attention have also been found recently in a Finnish study involving a computerised vigilance task. High susceptibles showed an increase in omission errors and greater variability in RTs from baseline to hypnosis, while low susceptibles

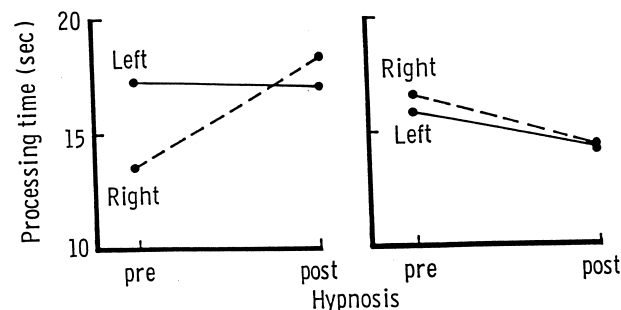
showed a reduction in errors and RT variance (Kallai, Revonsuo, Hamalainen, Markela & Gruzelier, 1998). Together these studies show that whereas susceptible subjects evinced inhibitory influences on attention with hypnosis, unsusceptible subjects improved attentional performance as the induction progressed.

### Anterior inhibitory processes

#### Left Anterior Inhibition.

Evidence of frontal inhibition was first disclosed by measuring right and left hemisphere processing times in dextral subjects with a haptic object sorting task comparing left and right hands (Gruzelier, Brow, Perry, Rhonder & Thomas, 1984). This was an extremely simple task involving the discrimination of letters and numbers. This was planned initially to validate asymmetries disclosed by the bilateral monitoring of electrodermal orienting and habituation processes described in the next section; in the haptic task which required "active" as distinct from "passive" touch, the mediation of hemispheric influences is unambiguously contralateral. Subjects sorted objects by class with each hand separately while blindfolded.

Hand order was counterbalanced and there was control for movement time. The task was done prior to hypnosis and again after the hypnotic induction, with susceptibility monitored through the experiment. As shown in Figure 4 high susceptibles showed an increase in right hand processing times with hypnosis while there was no change in their left hand times, nor were there bilateral changes in low susceptibles. The increase in the processing times of the right hand (indexing the left hemisphere) correlated positively with the hypnotic susceptibility score. Some evidence has suggested that the anterior inhibition may be laterally asymmetrical and biased towards the left hemisphere. We replicated the slowing of left hemispheric processing with hypnosis in high susceptibles in contrast to low susceptibles in a follow-up experiment with middle aged subjects, which was performed away from the laboratory and which included a non-hypnosis control group, (Gruzelier, Brow, Perry, Rhonder & Thomas, 1984). The combining of both experiment samples also disclosed evidence of a left hemispheric preference in high susceptibles at baseline as had been shown in the electrodermal study outlined in the next section.



**Figure 4:** Haptic processing times for right and left hands for prehypnosis baseline and with hypnosis in high (left figure) and low (right figure) susceptibles.



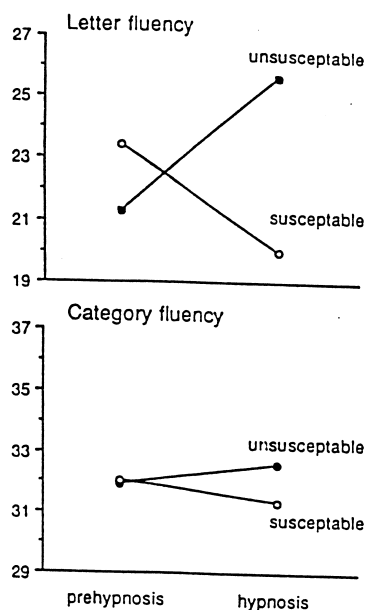
Left-sided inhibition of somatosensory functions was replicated further by examining haptic processing with an *active-alert induction* (Cikurel & Gruzelier, 1990). Following Banyai & Hilgard (1976) subjects pedalled a stationary exercise bicycle against a load and with instructions of mental alertness in the hypnotic induction. Dextral subjects were selected with the Barber scale to form groups of high and medium susceptibles. Each subject participated in two sessions, one involving the conventional relaxation induction and the other the active-alert induction. In both conditions a baseline measure was obtained either while seated or while pedalling. Session order was counterbalanced and in each session hypnotic susceptibility was monitored to validate the group designation and to compare the induction procedures, which in the event produced similar influences on susceptibility ( $r=0.79$ ,  $p<0.001$ ). As in previous experiments there was a hypnosis x hand interaction such that for the group as a whole there was a slowing of right hand processing times with hypnosis and no change with the left hand. Subdivision of the subjects into high and medium groups showed that whereas both groups shared the right hand slowing with hypnosis, the left hand of high susceptibles gave faster sorting times with hypnosis, whereas in medium susceptibles there was a bilateral slowing of processing. Comparing induction procedures, the active-alert induction shared with the conventional procedure the slowing of left hemispheric processing but the active-alert induction was solely responsible for the improvement in right hemispheric processing.

Lateralised anterior inhibitory functions were examined further with a small battery of neuropsychological tasks (Gruzelier & Warren, 1993). These included word and category fluency which are both left hemisphere tasks with word fluency left frontal and category fluency left temporal. Design fluency was included to index right anterior processing. Left and right

hand finger tapping was included to examine motor and pre-motor functions. Dextral subjects were first selected with the Barber scale and divided into high and low susceptibility groups. Susceptibility level was also monitored throughout the experiment. The influence of hypnosis on word fluency differed substantially between the groups. While low susceptibles showed an increase in fluency from the pre-hypnosis baseline with hypnosis, high susceptibles showed a decrease. While the groups did not differ at baseline in word fluency (though there was a mean advantage to high susceptibles) with hypnosis there was a highly significant difference between them. The semantic category test showed similar mean changes but did not disclose significant effects. These results are contrasted in Figure 5. With design fluency both groups showed an improvement with hypnosis whereas in finger tapping only the low susceptibles showed improvement in finger tapping – the high susceptibles showed an impairment. The word versus category fluency effects have now been replicated in the Finnish study mentioned above (Kallai, Revonsuo, Hamalainen, Markela & Gruzelier, 1998) which has brought together in one investigation opposite changes in susceptible and unsusceptible subjects, firstly in vigilance performance involving a thalamo-cortical (parieto-frontal) attentional network mentioned above and secondly in word generation involving the left prefrontal cortex.

Patterns of correlations between the fluency tasks supported an inhibitory influence of hypnosis centring on the left anterior word fluency performance. Firstly, the three fluency tests did not correlate at baseline implying an independence of function. Secondly, correlations between baseline and hypnosis conditions were significant for category fluency and design fluency but not for word fluency, in support of the word fluency test alone being altered by hypnosis. In contrast, significant correlations were obtained with hypnosis

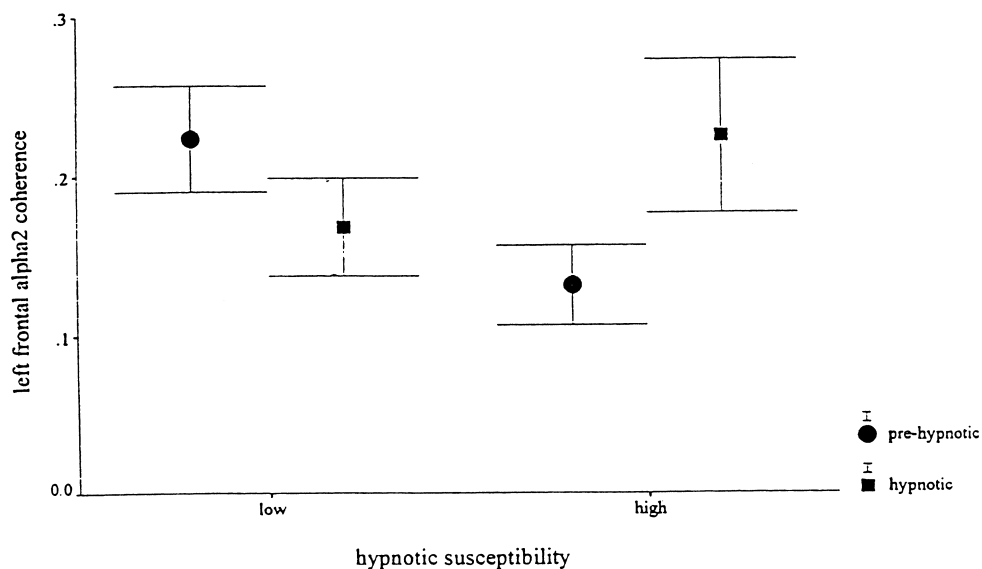
between word fluency and both design fluency and category fluency, but not between design and category fluency. This could be interpreted as showing that an underlying process such as distributed inhibition was most at work with word fluency, and while centring on left anterior processes was also having some impact on design and category fluency which involved right anterior and left temporal processing respectively. Correlations also showed that the significant relation between left and right hand finger tapping dexterity before hypnosis was reduced with hypnosis in keeping with a tendency towards lateral dissociation.



**Figure 5.** Word fluency for letters and categories in high and low susceptibles in prehypnosis baseline and with hypnosis.

Anterior disconnection with hypnosis in susceptible subjects was recently disclosed by Kaiser in an unpublished experiment involving EEG topographical mapping with a 32 electrode array in which we examined regional connectivity with EEG coherence. EEG coherence, a putative measure of connectivity, was examined between bipolar pairs of electrodes. This disclosed a significant hypnosis x group x condition interaction in high alpha activity, as shown in Figure 6. In high susceptibles with hypnosis there was a reduction in connectivity within the left prefrontal region - specifically between left lateral (FP1 and F7) and medial (F3 and FTC1) placements - whereas the opposite effect, namely an increase in connectivity was found in low susceptibles. In baseline there was also a highly significant difference between susceptibility groups in the direction of greater left anterior connectivity in high than low susceptibles.

Importantly the coherence result did not generalise to all bands but was restricted to high alpha activity. This represents an EEG band which relates to cognitive as distinct from conative processing, variously described as indexing high workload, sustained motor control and long term memory (Mecklinger & Bosel, 1989; Serman, Mann, Kaiser & Suyenobu, 1994; Klimesche, 1996; Burgess & Gruzelier, 1998). The importance of selectivity in narrow band EEG power has also been demonstrated by our differentiating hypnosis from relaxation with high theta versus low alpha band power (Williams & Gruzelier, 1998).



**Figure 6** Left anterior EEG coherence in baseline and hypnosis for medium/high and low susceptibles (high short distance coherence represents low connectivity and vice versa).

### Fronto-Limbic Supervisory Attentional System.

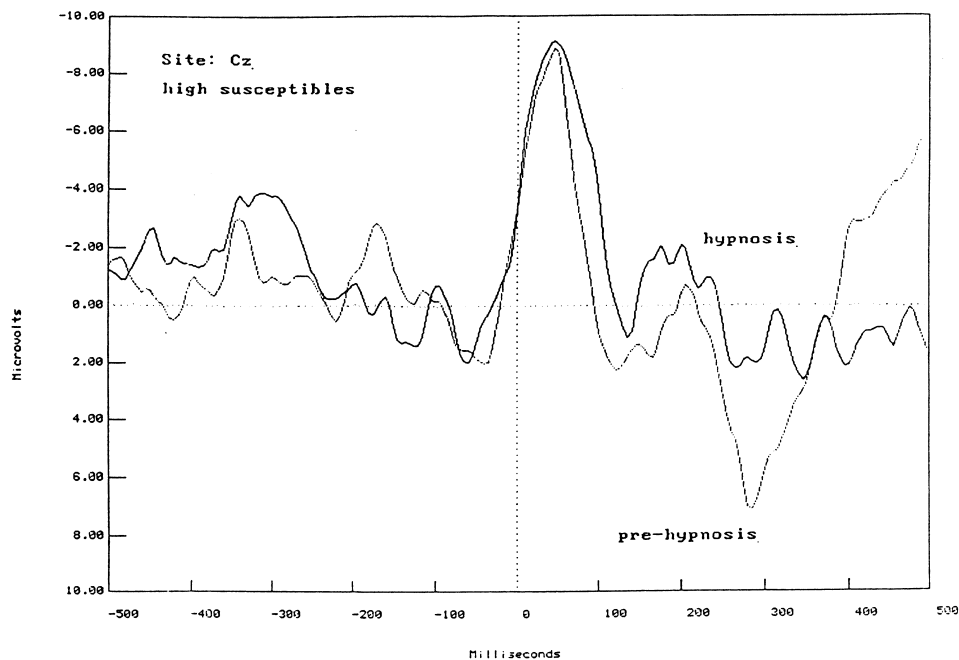
We went on to examine evidence of frontal inhibition in the context of contemporary models of anterior functions which focus on attentional control systems (Posner & Peterson, 1990; Shallice & Burgess, 1991). A supervisory attentional system which involves the frontal lobes and limbic system monitors ongoing activity and modulates behaviour in response to novelty, as in orienting, and when environmental stimuli convey conflicting information. We tested this with a behavioural and electrophysiological paradigm which requires the monitoring of errors in performance (Kaiser, Barker, Haenschel, Baldeweg & Gruzelier, 1997). We utilised a Stroop-like task involving a simple 2-choice reaction time task in which a button was pressed according to the side in which a green arrow was pointing (congruent condition). This was contrasted with a complex 4-choice task where in addition

to the green arrow condition red arrows were randomly presented, in which case the button must be pressed in the opposite direction to the arrow (incongruent condition). Electrophysiological evidence has shown that following an erroneous response in a reaction time task there is a large negative going wave at about 100msecs, referred to as error-related negativity and termed an *error detection wave*, which is not elicited following correct responses (Falkenstein, Hohnbein, Hoorman & Blank, 1990; Gehring, Goss, Coles, Meyer & Donchin, 1993). This negative wave is followed by a positive wave which varies with a range of task-related factors and may represent context updating, error evaluation and adjustment of response strategies, an *error evaluation wave* (Falkenstein, Hohnsbein & Hoorman, 1995).

With hypnosis the medium/high susceptibility group showed an increase in errors on incongruent trials –the stroop interference effect– but no change in errors on congruent

trials, whereas the performance of low susceptibles remained constant. Reaction times were not influenced by hypnosis in either group. Therefore in medium/high susceptibles there was a failure to inhibit the automatic response in keeping with an inhibition of frontal attentional control. However, the large negative going error detection waves that were elicited were non-significantly larger in the medium/high than the low susceptibility group, and these waves were unaltered by hypnosis. In other words an error detection system which operates at an early and possibly pre-conscious stage of processing was not

compromised by hypnosis; to wit the unconscious hidden observer of Hilgard, Morgan & McDonald (1975). In contrast we found that the positive going error evaluation wave following the error detection wave was reduced in amplitude with hypnosis but only in medium/high susceptibles. Results for the susceptible subjects are found in Figure 7. This was in keeping with inhibition of a frontal error evaluation process and was compatible with the behavioural data showing a higher error rate on incongruous trials in the medium/high susceptibles with hypnosis.



**Figure 7:** Error detection and error evaluation waves in medium/high susceptibles in hypnosis and pre-hypnosis baseline.

The error detection wave has been localised to a midline anterior cingulate generator (Dehaene, Posner & Tucker, 1994), a promising candidate for involvement in hypnosis.

The anterior cingulate performs executive functions which have been subdivided into affective and cognitive components (Devinsky, Morrell & Vogt, 1995). The cognitive

executive component is involved in response selection in advance of any movement and in cognitively demanding information processing such as Stroop interference, localised by blood flow imaging and lesion studies to the anterior cingulate (Pardo, Pardo, Janer & Raichle, 1990; George, Ketter, Parekh, Rosinsky, Ring, & Casey, 1994; Vendrell, Junque, Pujol, Jurado, Molet & Grafman, 1995), and by some to the right anterior cingulate (Bench, Frith, Grasby, Friston, Paulesu, Frackowiak & Dolan, 1993). The affective executive functions are involved in regulation of autonomic and endocrine functions, assessment of motivational context and significance of sensory stimuli and emotional valence. These are mediated through extensive connections with the amygdala and periaqueductal grey and autonomic brainstem nuclei. Our results have indicated that the monitoring of motor performance carried out by the cognitive executive component remained intact, for the error detection wave and RTs were unchanged by hypnosis. Rather it would appear that the affect system involving connections with the rostral limbic system including the amygdala was unresponsive, as shown by the absence of the error evaluation wave and apparently motivational influences on performance. This interpretation is also in keeping with the reduced electrodermal orienting activity reflecting a reduction in amygdaloid excitatory modulatory influences. Dissociation between cognitive and affective anterior cingulate executive systems would explain the increase in the Stroop interference effect with hypnosis.

### **Summary**

Further evidence of a selectivity of neurophysiological action of hypnosis was shown through examination of anterior inhibitory influences:- 1) the dissociation between error detection and error evaluation waves; 2) the left lateralised influences on haptic processing and

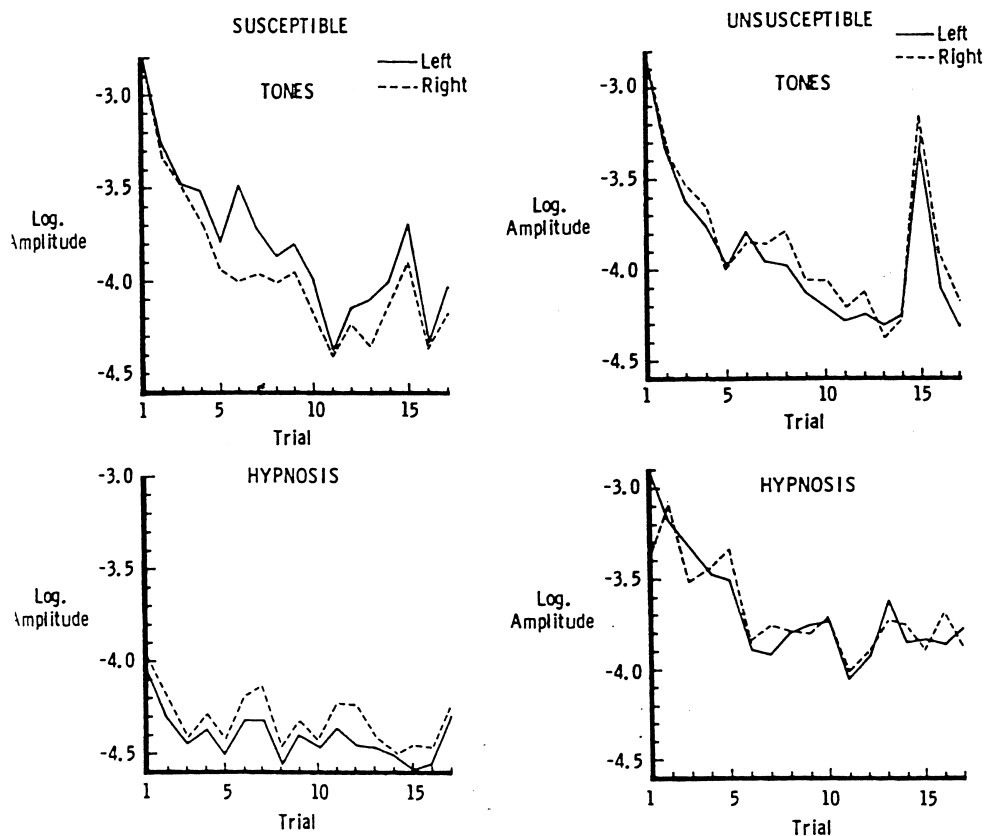
the improvement in right-sided processing that was specific to the active-alert induction; 3) the specificity within the left hemisphere for the effects on verbal fluency which were restricted to letter and not semantic designated categories; 4) the localisation of the changes in EEG coherence to within the left frontal lobe; 5) the restriction of the EEG coherence changes to the high alpha band. These factors serve to introduce a note of caution in attempts to interpret changes in brain blood flow and metabolism in hypnosis which do not permit such fine grained interpretation, nor do they discriminate between facilitatory and inhibitory functional systems.

### **Right-sided processing.**

Focal versus distributed influences of hypnosis have also been demonstrated in experiments investigating the popular view of right hemispheric involvement in hypnosis (Pedersen, 1984). Firstly, in our original experiment on electrodermal orienting and habituation processes (Gruzelier and Brow, 1985) bilateral recording disclosed an asymmetry in the amplitude of orienting responses favouring the right hand in hypnosis in high susceptibles whereas there was no reliable asymmetry in low susceptibles. This was in contrast to the baseline session where after the initial tones there was an asymmetry favouring the left hand in high susceptibles and again no reliable asymmetry in low susceptibles; the initial stage of orienting is thought to involve the right hemisphere which governs states of broadened attention, after which the focal and selective attentional abilities of left hemisphere take over as would be exemplified in the high susceptibles with their left preference after the initial trials (see Figure 8). At the time the psychophysiological experiment was done the mediation of hemispheric influences on electrodermal activity was considered controversial. Subsequently the influence of limbic

modulation has been clarified by intracranial stimulation studies (Mangina and Beuzeron-Mangina, 1996) which have supported the original interpretation of the dominance of ipsilateral limbic modulatory influences on the passive orienting processes (Gruzelier, 1973). Therefore the results may be interpreted as showing a left hemispheric preference in high susceptibles at baseline. While this result was not predicted and ran counter to right hemisphericity theories of hypnotic susceptibility, support was forthcoming from

the subsequent investigation of lateralised haptic processing described above (Gruzelier, Brow, Perry, Rhonder & Thomas, 1984). Such baseline left hemispheric advantages may simply reflect greater cognitive agility in line with task demands by high susceptibles (Crawford, 1989). Accordingly it would appear that it was the hypnotic induction that instated the right hemispheric functional preference in susceptible subjects.



**Figure 8** The amplitude of bilateral electrodermal orienting responses showing reversal of asymmetry from baseline (tones) to hypnosis in high susceptibles and no consistent changes in low susceptibles.

An enhancement of right posterior functions was found in an experiment involving

the divided visual field presentation of flashes requiring brightness judgements. The experi-

ment involved three sessions in the order baseline, hypnosis, baseline. It was conducted with eyes open with sufficient trials to perform signal detection analysis to give estimates of perceptual sensitivity independent of cognitive bias (McCormack and Gruzelier, 1993). Blocks of trials were interspersed with a live hypnotic induction. Susceptibility was monitored throughout the experiment with subjects divided into medium and high susceptibles. Results are shown in Figure 9. Perceptual sensitivity was found to be enhanced in the hypnosis condition compared with the control conditions. Comparison of the susceptibility groups indicated a bilateral increase in perceptual sensitivity in medium susceptibles whereas in high susceptibles there was no change in susceptibility in the left hemisphere (right visual field) in contrast to a focal right hemispheric enhancement (left visual field). An improvement in perceptual sensitivity is according to signal detection theory indicative of an increase in signal to noise ratio as will occur with a reduction in central levels of arousal. Analysis of the cognitive bias variable

showed that judgements were more conservative for the right hemisphere than the left for the group as a whole ( $p < 0.05$ ). However, there was no effect of group, providing no evidence for the possibility that the influence of hypnosis may be due to a shift in attitude such as an adoption of a lax response criterion leaving perceptual sensitivity unaffected (Naish, 1985). The demonstrable changes in perceptual sensitivity with hypnosis were consistent with other reports (Segal & Fusella, 1970; Miller & Leibowitz, 1976; Farthing, Brown & Venturio, 1982). Thus the results which disclosed an enhancement of right posterior processing with hypnosis, showed that only in high susceptibles was this strictly lateralised. It was more widely distributed in medium susceptibles to include a bilateral processing enhancement and was of lesser magnitude. A similar conclusion was reached in a haptic sorting task experiment above (Cikurel and Gruzelier, 1989).

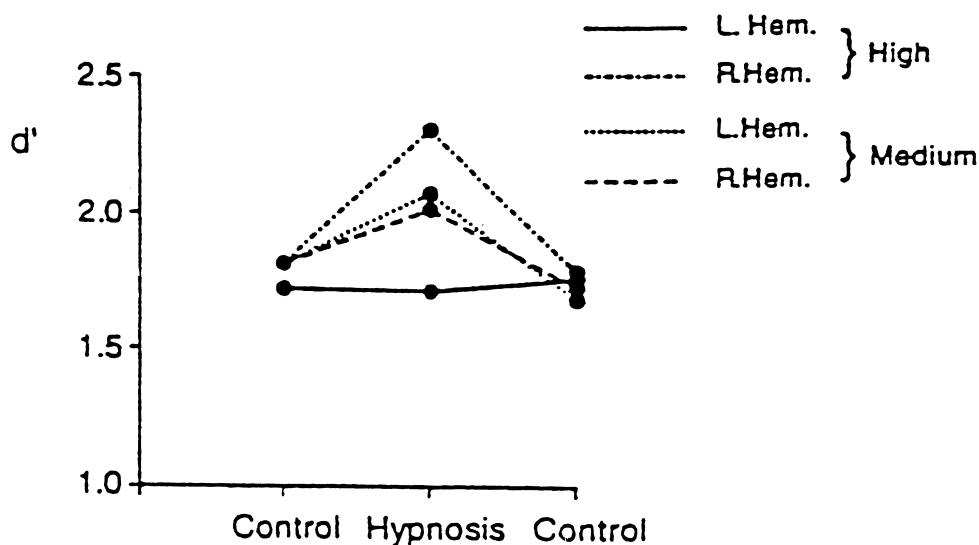


Figure 9: Visual sensitivity in baseline control conditions and hypnosis in high and medium susceptibles for left and right hemispheres.

Turning to central and temporal regions, an electrophysiological study was performed measuring evoked potentials to tone probes presented simultaneously with the hypnotic induction and compared with their presentation during a story read by the hypnotist. Event-related potentials in both conditions were referred to a baseline condition giving three conditions in all (Jutai, Gold, Thomas & Gruzelier, 1993). Bilateral electrode placements included central and temporal sites and the analysis centered on the N100 attentional component. According to assessment of hypnotic susceptibility monitored throughout the study subjects were categorised as low or medium/high susceptibles. Specific to the hypnosis condition there was a right>left asymmetry at the temporal location (electrodes T3/4) in the medium/high group. In contrast there was an opposite left>right asymmetry in the story condition of medium/high susceptibles, as well as in both the conditions of the low susceptibles. This reversal of asymmetry to favour the right hemisphere in susceptible subjects did not extend to the lateral central (C3/4) placements. The results demonstrated that right anterior temporal lobe activity was raised in medium/high susceptibles with hypnosis.

### Summary

The asymmetries in electrodermal orienting responses and the cortical evoked potential N100, both to auditory stimuli presented during the latter part of the induction (Gruzelier & Brow, 1985; Jutai, Golds, Thomas & Gruzelier, 1993) indicate a shift in the balance of temporal-limbic activity to favour the right hemisphere. In contrast the asymmetry of visual sensory sensitivity assessed with signal detection analysis (McCormack & Gruzelier, 1993) depicted an enhancement of right

hemispheric processing in high susceptibles and no change in the left hemisphere whereas medium susceptibles showed bilateral improvement.

## Self hypnosis and the immune system

### Examination Stress

Encouraged by the demonstrable influences of hypnosis on the central nervous system, we have examined the efficacy of self hypnosis training in buffering the effects of stress on the immune system in normal subjects, and in up-regulating the immune system in patients with immune compromise. We first set out to examine Kiecolt-Glaser's finding of a positive correlation between the amount of self hypnosis training at exam time in students and their CD4 T-lymphocyte counts (Kiecolt-Glaser et al, 1986). We compared with 12 controls 16 students who received our relaxation induction to which was added guided imagery of enhanced immune function, ego strengthening, feelings of happiness, and improved concentration. We controlled for frequency of practice in order to avoid a potential confound, namely that the effect could simply relate to personality differences associated with enthusiasm for practising self hypnosis. The hypnosis group was divided into high and low susceptibles on the basis of the Harvard group scale, while the control group covered the full range of susceptibility. There were ten sessions of hypnosis, one given live and the others tape recorded and practised three times a week at home.

An immune assay was repeated twice, once before training and once during the exams. The assay included Natural Killer (NK) cell counts, and counts of CD2, CD4 and CD8 T-lymphocytes, and the B-lymphocyte CD19. Cortisol was also assayed. Personality was



measured with the personality syndrome questionnaire (PSQ, Gruzelier et al, 2000a) with active, withdrawn and unreality syndromes. Withdrawal has been associated with immune compromise and there is little formal documentation relating to positive attributes of personality in relation to immune function. We hypothesised that the active personality would be associated with immune up-regulation. Life-style changes at exam time were monitored with a questionnaire and mood was measured with the Spielberger and Thayer scales.

NK cell counts and CD8 counts were found to decline in controls, but this decline did not occur in the hypnosis group ( $p < 0.002$ ;  $p < 0.07$ ) (Gruzelier et al, 2000b). Self-hypnosis was accompanied by a paradoxical increase in cortisol. These changes were significantly correlated suggesting an integrated pattern and underlying process. The effects were independent of life-style changes. Furthermore exam NK cell counts correlated positively with energy for the group as a whole and negatively with anxiety.

Additional benefits associated with hypnosis included higher energy ratings at exam time than in the control group ( $p < 0.01$ ), while increased calmness after hypnosis training correlated positively with increased CD4 counts ( $p < 0.01$ ). In controls cortisol correlated positively with tiredness and with an increase in anxiety ( $p < 0.035$ ,  $p < 0.009$ ). These congruent relations between cortisol and negative mood were not found in the hypnosis group suggesting that along side the paradoxical increase in cortisol in the hypnosis group, hypnosis results in a dissociation of the negative effects of cortisol (Gruzelier et al, 2000c).

Compelling relations were found between the personality syndromes of the group as a whole and the T and B-lymphocyte changes. The syndrome we predicted to be associated with immune up-regulation, namely the active syndrome, correlated positively with the full

range of lymphocytes assayed ( $p < 0.04$ - $p < 0.008$ ).

In a subsequent, as yet unpublished study (Gruzelier, Levy, Henderson), with a similar study design we compared a passive ( $N = 11$ ) versus active induction ( $N = 11$ ) and control condition ( $N = 6$ ). The "active" induction was similar to before, having immune-related imagery and ego strengthening suggestions, whereas the "passive" induction involved only the typical relaxation induction as used in our laboratory studies. Here the passive imagery group showed a marked decline ( $p < 0.008$ ) in CD4 counts at exam time, whereas the decline was not significant in the active imagery group ( $p < 0.27$ ). Regarding the relevance of the CD4 marker to the health of students at exam time, eight students reported illnesses around the exam period. When comparing them with the remainder, the illness group had a significant decline in CD4 counts ( $p < 0.016$ ) whereas the decline was not significant in the well group ( $p < 0.15$ ). In other words the beneficial influences of hypnosis were relevant not only to well being, but also to health. We went on to explore these relations in a clinical study.

### **Recurrent and chronic genital herpes**

The first association between psychological distress and reduced resistance to HSV was reported by Lycke et al (1974) in the form of increased antibodies to the latent herpes viruses HSV, Epstein-Barr virus and Cytomegalovirus in depressed patients. Subsequent investigators confirmed this association in medical students at exam time and in spouses about to divorce, in whom in addition there was a reduction in Natural Killer (NK) cell activity, CD4 lymphocyte counts and lymphocyte proliferative responses (see Sheridan et al, 1994). NK cells, macrophages, CD4 and CD8 lymphocytes, interferon alpha and gamma, interleukin 2 (IL-2) and leucocyte migration inhibitory factor are all significant in protecting

against HSV (Rinaldo and Torpey, 1993).

20 patients with frequently recurrent genital herpes (HSV-2) attending a department of genito-urinary medicine at Chelsea and Westminster Hospital were examined at baseline and after a six week course of self hypnosis (Fox et al, 1999). All were due to discontinue prophylactic antiviral medication for a trial period or were reluctant to take the medication. Patients had experienced a median of 12 or more episodes a year

Overall the number of recurrences fell following hypnosis training ( $p < 0.048$ ). The median number in the six weeks before was 2 (range 0 – 6) and in the six weeks of self hypnosis 1 (range 0 – 3). The patients were subdivided into Improver ( $N = 13$ , 65%) and Nonimprover ( $N = 7$ , 35%) groups on the basis of clinical outcome. There was no difference in Barber suggestibility scores between the groups; the mean score was 4.8, and the pre-intervention number of recurrences was higher in those who improved (2.5 versus 1.35), but not significantly so. The number of recurrences fell in the Improver group to 0.84 ( $p < 0.001$ ), and increased in the Nonimprovers ( $p < 0.03$ ). The number of symptomatic days fell in Improvers and rose in Nonimprovers ( $p < 0.002$ ).

Following hypnosis Natural Killer cell counts increased only in Improvers ( $p < 0.02$ ), as did functional NK activity with regard to HSV specific Lymphokine Activated Killer (LAK) following activation by interleukin-2, which more than doubled ( $p < 0.007$ ). The rise in percentage of NK cells as a proportion of the total lymphocyte count ( $p < 0.015$ ) was matched by a fall in CD4 lymphocytes ( $p < 0.03$ ). CD3 and CD8 lymphocytes increased for the group as a whole (both  $p < 0.02$ ), suggesting a nonspecific influence of hypnosis independent of HSV. Cortisol remained unchanged, as did HSV specific NK and Antigen Dependent Cellular Cytotoxicity. Correlations were obtained between the Bar-

ber scale and the dependent variables. Suggestibility correlated positively with an increase in NK cell counts ( $p < 0.03$ ), CD3 counts ( $p < 0.01$ ) and CD 8 counts ( $p < 0.02$ ).

The patients were also examined on the Hospital Anxiety and Depression Scale (HAD) at the beginning and end of the study. Improvers showed a reduction in both depression and anxiety when compared with Nonimprovers ( $p < 0.05$ ). In support of our student study an action-orientated personality, measured with the PSQ was associated with improvement ( $p < 0.04$ ) while a withdrawn personality was associated with nonimprovement ( $p < 0.04$ ).

In the year following the study some patients have remained off medication and have experienced very little recurrence of HSV. This pilot study requires confirmation in a controlled clinical trial, but confirms that relaxation can improve nonspecific NK cell function, and as shown by others can reduce antibody titres to HSV (Kiecolt-Glaser et al, 1985; Zachariae et al, 1990). Hypnosis, however, is more than relaxation (e.g., Gruzelier and Brow, 1985; Williams and Gruzelier, 2000). This clinical study has demonstrated for the first time that hypnotherapy may bring about an improvement in a chronic medical condition.

## Conclusion

This series of experiments has shown a number of reproducible changes in brain function which distinguished medium to high susceptibles after instructions of hypnosis both from their baseline state and from low susceptibles. The attempts were modest in scope and must be confined to the traditional hypnotic relaxation induction. Continuing support was provided for associations between hypnosis and: 1) activation of anterior fronto-limbic inhibitory processes, 2) anterior inhibition or disconnection, either lateralised to left hemi-

spheric regions or bilateral depending on the processes examined, 3) involvement of right temporoposterior processing, 4) evidence of superior attentional abilities in high susceptibles, 5) evidence of poor attentional abilities in unsusceptible subjects with progressive improvement through the induction, and 6) no evidence of right hemisphericity in the baseline state in susceptible subjects.

As the studies unfolded a selectivity of central action increasingly became a hallmark of hypnosis providing undeniable evidence of neurophysiological changes in susceptible subjects which distinguished them from unsusceptible subjects. Across electrodermal, electrocortical and behavioural domains susceptible subjects evinced inhibitory influences on attention with hypnosis whereas unsusceptible subjects improved attentional performance as the induction progressed. Evidence was also found for bilateral alterations of function in medium susceptibles in situations where changes in high susceptibles were lateralised, suggesting more diffuse or distributed changes in medium susceptibles and more focal changes in high susceptibles. Together these results indicate the importance of stratifying groups into low, medium and high susceptibles.

In our neuropsychological translation of the traditional hypnotic induction, hypnosis was initiated by engaging anterior executive control systems. Aside from alterations in cortical functions along anterior-posterior and lateral axes, these will orchestrate top down changes influencing thalamic and brain stem mechanisms. Currently there is renewed interest in the electrophysiology of thalamocortical mechanisms in perceptual binding, conscious perception and altered states of awareness (Llinas & Pare, 1991; Singer, 1993). Llinas, Joliot & Wang (1994) have proposed that consciousness is a noncontinuous event determined by simultaneity of activity in specific thalamocortical nuclei which provide the

content of experience, and the nonspecific diffuse thalamic projection system which provides the context and alertness. In this regard the anterior and posterior cingulate appear of particular promise in the top down control of thalamic activity relevant to hypnosis. Devinsky, Morrell & Vogt (1995) have remarked "One of the unique features of anterior cingulate cortex circuitry is its diverse thalamic afferents and consequent ability to sample inputs from more thalamic nuclei than any other cortical region. The ability to sample from a wide range of thalamic inputs may be crucial for its contributions to motor response selection functions. p 280" The same could be said for connative functions and the limbic thalamus (Bentivoglio, Kultas-Ilnsky & Ilnsky, 1993). Hypnosis research would benefit from examining the interplay between cortical and thalamo-cortical systems, for which the methodology of fast frequency EEG transients holds much promise.

In Llinas's model dreaming is regarded as a state of hyperattentiveness to intrinsic activity without the registration of sensory input, a state with an obvious affinity with hypnosis. This serves to acknowledge that the dream analogy remains appealing for aspects of the hypnotic experience. Consider Fuster's (1995) description of cognitive features of dreaming which include the altered sense of time and absence of temporality, the lack of guiding reality and critical judgement, the anchoring in personal experience, affective colouring, dissociation from sensory input and context. "The fragmented networks activated in the dream seem to lack the associative links to a time frame, anchored as they are in the present, without time tags and references." This could equally be a description of the hypnotic state as high susceptibles experience it.

Self-hypnosis with guided imagery directed to both healthy immune function and towards mobilising resources, in three studies was found to be effective in buffering negative

influences of stress on the immune system, which in one was combined with a chronic medical condition. The 10 session programme was successful in overcoming initial differences in susceptibility. It was of relatively short duration, was inexpensive and through home practice was saving of clinical time. Guidance for individual differences in patient response and compliance may follow the predictive ability of the personality trait. Given the influence of hypnosis in buffering the decline or raising the natural killer cell population, which has antiviral and anti tumor functions, this relatively simple and inexpensive psychological intervention has applications both to a range of immune disorders and for

promoting health in the population at large.

In conclusion, as Schopenhauer remarked "All truth passes through three stages. First it is ridiculed. Second it is violently opposed. Third it is accepted as being self-evident". Application of the rapid advances in cognitive neuroscience to hypnosis research may make the reality of the third stage ever more likely.

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