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Contemporary Hypnosis and Integrative Therapy is the official publication of the British Society of Clinical and Academic Hypnosis and the European Society of Hypnosis in Psychotherapy and Psychosomatic Medicine, published on a quarterly basis. The intention of the journal is to provide a forum for the presentation and discussion of theory, research, and professional practices in the field of hypnosis and integrative therapy, with the general aim of furthering scientific understanding of the phenomenon and promoting informed and responsible use of hypnotic and consonant procedures.

The subject matter of the journal is defined by the practices, phenomena, theory, and research associated with the term ‘hypnosis’ since the middle of the nineteenth century. Articles on topics related to hypnosis will be considered in so far as they help to further the understanding of the nature and function of the basic phenomena; such topics might include, for example, physiological processes, sleep and dreaming, altered states of consciousness, imaginative processes, including imagery, absorption, and fantasy, role-playing, compliance, and obedience. Contemporary Hypnosis and Integrative Therapy welcomes research papers, case studies, reviews, etc., relating to the professional employment of hypnotic procedures and consonant interventions in clinical, educational, occupational, forensic, medical, and dental work.

Contemporary Hypnosis and Integrative Therapy is essential reading for anyone interested in contemporary research, ideas, and clinical practice in the field of hypnosis and integrative therapy.
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EDITORIAL COMMENTARY: A TRIBUTE TO GIANCARLO CARLI

ENRICA LAURA SANTARCANGELO, MANFRED ZIMMERMANN, JOHN GRUZELIER

1Department of Physiological Sciences, University of Pisa, Italy; 2Neuroscience and Pain Research Institute, Heidelberg, Germany; 3Department of Psychology, Goldsmiths, University of London, UK

On November 20th 2010, a meeting in honour of Giancarlo Carli was held in Siena (Italy). The congress (Figure 1), organized by Carli’s friends and colleagues from Europe, Canada and the USA on the occasion of his retirement had the title (‘Pain, Hypnosis and Sport Physiology: A Tribute to Giancarlo Carli’) referring to Carli’s multifaceted scientific career (www.giancarlocarli.com), which includes a deep interest in human hypnosis. This issue of Contemporary Hypnosis collects the laudation of Manfred Zimmermann, papers presented at the meeting, and other contributions that could not be included in the congress programme. Altogether, the papers show that different scientific interests have been efficaciously merged in the activity of Carli, and that very different personalities and sensibilities have been deeply influenced by him. Following his ideas, he has inspired an integrated approach to medicine at academic, educational, and institutional levels.

Giancarlo Carli (Figure 2) was trained in the laboratories of Giuseppe Moruzzi, in Pisa, where he began his research on animal hypnosis, and of Vernon Mountcastle, in Baltimore, where he was involved in experiments of somato-sensory physiology. He was attracted very early on by the study of pain, in which he could combine his neurophysiological education with a growing interest in cognition and behaviour. Pain has been his main line of research (see contributions of Lefebvre, Bachiocco, Diers & Flor and Mongini), developed with both animal and human models, but he has also been enthusiastically involved in research on human hypnosis (De Benedittis, Jensen, Santarcangelo and Finer), while his interest in cognition left its stamp on the Department of Sports Physiology he founded at the Institute of Physiology of Siena (Fontani & Migliorini).

In the 1970s, Giancarlo Carli was engaged in studies on tonic immobility (Farabollini), also named ‘animal hypnosis’, and his curiosity induced him to investigate the commonalities of animal and human hypnosis. In reading about human hypnosis and discussing his opinions with leading researchers in the field, he understood very quickly that tonic immobility was a phenomenon quite different from human hypnosis. However, he was captured by the sparkling atmosphere of the rise of experimental hypnosis and received a sort of commitment—‘maybe a hypnotic suggestion’—from Martin Orne who, being sceptical about the existence of the ‘hypnotic state’, called for physiologists to join in researching hypnosis.

Some years after, Carli was able to start with experimental trials on the physiological correlates of hypnotisability and hypnosis (Santarcangelo), at the Institute of Physiology of the University of Siena, where he has been serving as Full Professor and Head of Department for several decades (Aloisi).
Giancarlo Carli has the merit to have understood that multidisciplinary research allows the best approach to hypnosis (Aloisi and Fontani & Migliorini), and to have encouraged his collaborators to address frontier topics courageously (Bachiocco and Santarcangelo). In particular, his open-minded approach to neuroscience has allowed him to confront the prejudices of many scientific arenas against hypnosis, and, later, to focus his studies on aspects of hypnotisability not stringently related to the ability to experience the hypnotic trance (Santarcangelo), which may appear quite unorthodox.

This issue of *Contemporary Hypnosis and Integrative Therapy* is a tribute to Professor Carli as a physiologist and a man who has gone through life and work with intellectual independence, modesty, courage, and fun. We hope Giancarlo goes on with research with his usual gentlemanly style. On the other hand, we hope that the story of his scientific career and of his influence on the activity of many colleagues may encourage young researchers to follow their own curiosities even when these are far from the fashion of the moment.
EDITORIAL COMMENTARY: A TRIBUTE TO GIANCARLO CARLI

University of Siena
Department of Physiology

Pain, Hypnosis and Sport Physiology
A Tribute to Giancarlo Carli

Siena, S. Maria della Scala, November 20th, 2010

Figure 1. Details of the meeting held in honour of Giancarlo Carli
Figure 2. Giancarlo Carli
LAUDATIO ON PROFESSOR GIANCARLO CARLI: ON OCCASSION OF HIS RETIREMENT FROM ACADEMIC DUTIES

MANFRED ZIMMERMANN

University of Heidelberg

Key words: hypnosis, animal hypnosis, pain, neurophysiology, neuroendocrinology

It is my pleasure to pay tribute to Professor Giancarlo Carli, in view of his creative and multifaceted contributions to the neurosciences for more than 50 years. Essentially: all of Carli’s work was never l’art pour l’art just to produce sophisticated science concepts, but in all his fields the ultimate aim in his experimental and clinical research was to help suffering human patients.

In 1959, at the age of 21, Carli entered the Physiology Laboratory of Siena University as a medical student, and was immediately set alight by science—obviously this was a key event in determining his subsequent life, a career as a neurophysiologist. His first publication was published in *Science* (Carli et al., 1963), reporting on central pathways controlling the recently discovered rapid eye movement (REM) sleep. Seeing his publication in one of the most prestigious scientific journals must have been a tremendous reward for the young author and certainly reinforced his motivation to carry on in the neurosciences.

An interlude followed in the USA from 1969 to 1971 when Carli spent a training fellowship on the psychophysics and neurophysiology of skin mechanosensation at Johns Hopkins University in Baltimore, in the group of Vernon Mountcastle at the Department of Physiology. Carli and LaMotte studied the threshold sensation of the hand in humans and monkeys via the frequency of vibratory stimuli, showing virtually the same quantitative stimulation-response characteristics in both species (Mountcastle et al., 1972). This work became fundamental to the contributions of Meissner’s and Pacinian corpuscles and their afferent nerve fibres in low versus high frequency sensation, and is referred to in some textbooks on the somatosensory system.

From 1965 Carli continued his sleep research at the famous Institute of Professor Giuseppe Moruzzi at Pisa University, with Ottavio Pompeiano as his supervisor. Moruzzi’s research focus was on the non-cognitive functions of the nervous system, such as the sleep–wake cycle, the mechanisms and control of electroencephalography (EEG), the origin of emotions and motivations, and levels of consciousness, which he attributed to the ascending reticular activating system (ARAS) in the brainstem reticular formation and hypothalamus. This novel concept had been introduced through a seminal publication by Moruzzi and Magoun in 1949.

Working in the intellectual environment of a worldwide famous institute obviously was a favourable condition for Carli to become involved in several research projects, as is reflected in a total of 17 publications that appeared in 1966 and 1967, in 12 of these Carli was the first
author. One of the novel results was that afferent somatosensory information transmission was blocked during phases of REM sleep, and that the mechanism of presynaptic inhibition was responsible for sensory control during sleep states (Carli et al., 1966). At this time our group in Heidelberg was studying the functional role of spinal presynaptic inhibition in tactile sensations, and we noticed with great interest the report from Pisa strongly supporting the physiological importance of this novel inhibitory mechanism in relation to sleep states. For his early contributions to the understanding of sleep mechanisms Carli was awarded a Pioneer on Sleep Studies by the Sleep Research Society in 2003.

In 1967 Carli was invited by Professor Moruzzi to set up a new laboratory on hypnosis in animals. The label of hypnosis in animals was used for a state of tonic immobility that was induced, for example, in rabbits by laying them on their back. In this abnormal position animals remained immobile for minutes, with all mono- and polysynaptic motor and righting reflexes totally suppressed. Animals even showed neither convulsive movements during evoked brain seizures documented in the EEG nor escape reactions to painful stimuli—thus motor behaviour was totally suppressed during this state of immobility.

Carli alluded to the potential survival value of this immobility reaction, an aspect studied many years later (e.g. Fanselow & Helmstetter, 1988) as freezing reaction. David Livingstone (1872) reported an attack by a lion during an expedition in Africa: ‘I saw the lion just in the act of springing upon me, and we both came to the ground together. The shock produced a stupor similar to that which seems to be felt by a mouse after the first shake by a cat. The shake annihilated fear, and allowed no sense of horror in looking around at the beast. The peculiar state is probably produced in all animals killed by carnivores.’ Today this behavioural state is considered as an innate protective reaction in some extremely life threatening situations (e.g. an encounter with a predator), and this behaviour is therefore also termed a death feigning reaction (see Lefebvre, this issue). Pharmacological studies in Carli’s group revealed that endogenous opioids were not involved in tonic immobility.

From 1978 onwards intensive study with Francesca Farabollini was aimed at identifying the endocrinological changes associated with animal hypnosis (reviewed by Farabollini, this issue). They found that corticosterone and testosterone levels essentially remained stable during the state of hypnotic immobility, suggesting a kind of functional endocrine buffer working to maintain endocrine balance, in spite of the presence of a stressful situation. This neuroendocrine stability differentiates the hypnotic state from the alternative emergency reaction as originally described by Cannon (1915), and is associated with huge activation of the hypothalamic-pituitary-adrenal axis paralleled by autonomic and motor defence reactions.

The condition and accompanying electrocortical phenomena of tonic immobility in animals suggest some similarity to catalepsy in humans. Carli and Lefebvre (reviewed by Lefebvre, this issue) pointed to another protective behaviour observed during childbirth in monkeys where the mother remains silent in spite of great pain during parturition: crying as a normal reaction to pain would attract predators and thus endanger the lives of the mother and newborn. In 1969 Carli received an award by the American Institute of Hypnosis for his early studies on animal hypnosis.

Work on animal hypnosis continued until 1984 and was followed in 1989 up until now by a study of physiological factors associated with hypnotic susceptibility in humans, a project which began with the thesis of Enrica Santarcangelo (Santarcangelo et al., 1989) and is still continued by her, in cooperation with Carli. Human subjects were classified by their high ver-
sus low capability to enter into a state of hypnosis. These studies revealed that hypnotizability in humans was associated with differences, for example, in spinal motor reflexes, postural and locomotor control, the preference for specific imagery modalities, the embodiment of imagery, and also in the cardiovascular effects of nociceptive stimulation (Santarcangelo et al., 2008). While classically the understanding and theory of hypnosis in humans had been largely based on psychodynamic theories, the studies by Carli and Santarcangelo helped disclose the importance of neuro- and psychophysiological factors as causative or modulatory mechanisms. Their findings imply suggestions for new therapeutic approaches using hypnosis as a medical tool.

Interestingly, James Braid, a founder of hypnosis in the 19th century, conceived that his novel therapy was based on psychological phenomena rooted in multiple physiological processes. Prior to Braid, Franz Anton Mesmer in the 18th century had suggested that magnetic forces originated from the doctor and were transmitted to the patient to induce healing. Thus Mesmer was convinced of a physiological process involved in the transmission of therapeutic effects from the doctor to patient, although his tenet of ‘animal magnetism’ was declared a misconception by the Société Royale in Paris. With approaches such as those of Carli and Santarcangelo, physiological processes are returning to the basis of hypnotherapy in the 21st century, and will hopefully contribute to the understanding of some of the underlying mechanisms. For advancing the concepts of hypnosis Carli was awarded honorary membership of the Italian Medical Association for the Study of Hypnosis.

In 1988 pain research appeared in Carli’s bibliography. Obviously the focus on pain emerged from his previous projects, which had included the interference of pain stimuli on sleep and hypnosis in animals. Now the formalin test was applied to induce pain behaviour in animals in a controlled way, initiating a long period of pain studies on animals. In addition, Carli’s research projects on human pain recently became of great significance in the prevention and treatment of pain in patients, as detailed below.

One of the innovative animal studies by Carli, together with Francesca Farabollini, was on the effect of prolonged pain on social behaviour and hierarchy in a group of rabbits housed in a natural environment (Farabollini et al., 1988). Formalin pain was induced in the dominant male. In spite of the dramatic decrease in motor and social activities due to the pain, the social ranking order of the animals was not eliminated, although the amount of aggressive actions was much reduced in the dominant animal, but not in the other group members. In conclusion, at least for the initial two days, persistent pain was not able to affect the pre-existing territorial situation and rank orders within the group; flight behaviour was maintained in subordinates, while the social activity of the whole colony sharply decreased.

One of their projects, in collaboration with Anne Gabriel at Maastricht University, studied the effect of environmental social and physical enrichment in rats, using subcutaneous formalin to induce a pain status of several hours in duration (Gabriel et al., 2010). The duration of mechanical allodynia was maximal in rats housed in a restricted environment and was reduced to a lesser extent in rats housed in an enriched environment (physical and/or social). In particular it was shown that increasing the physical activity of the animals resulted in a concomitantly larger reduction of the duration of mechanical allodynia, anticipating applications for physical and mild sporting activities in humans to prevent and treat musculo-skeletal pain.

In 1988 Anna Maria Aloisi became involved in Carli’s animal pain research, culminating in two comprehensive review articles on complex pain behaviour and its neuroendocrinological
background following tonic pain (Carli & Aloisi, 1993; Aloisi & Carli, 1996). From this cooperation, Aloisi’s own project on the sexual differences in pain mechanisms and behaviour emerged.

In the 1990s Carli, as a neurophysiologist, had a leading role in two remarkable clinical projects: the post-surgery care of patients without using opioid analgesic drugs and the study of patients with fibromyalgia syndrome (FMS) to reinforce the experience of well-being and countering pain.

The standard post-operative care of patients recovering from major surgery (i.e. thoracotomy) usually includes analgesic treatment with opioids. Carli learned from the Bologna University Department of Surgery that patients were offered post-surgery recovery with no use of opioid analgesics. Instead, patients received intensive social support, including visits by their family, to create a psychological setting in which the patient’s expectation was strengthened as a means for the self-control of pain. These principles are in line with factors determining the placebo effect, which were studied by Benedetti’s group at the University of Turin (Lui et al., 2010). This work revealed that the level and persistence of placebo analgesia is associated with the patient’s expectations and learning from previous experience of pain and pain control. Thus Carli, in cooperation with Valeria Bachiocco from the Bologna Clinic, assessed patients with questionnaires to predict individual levels of perceived pain and their potential to stay without opioid analgesics. The Ethical Committee of the International Association for the Study of Pain (IASP) recommended publication of the manuscript which was submitted to the journal *Pain*, as a case of a distinctive ethnic feature in handling pain. However, the editor of *Pain*, disregarding the *votum* of the Committee, rejected the manuscript because of ethical concerns, claiming that patients were inadequately treated for their pain. As a consequence, as chairman of the Ethical Committee of IASP, I stepped back as an expression of my protest against the editor’s verdict. Fortunately the work by Bachiocco and Carli was published in other distinguished pain journals (e.g. Bachiocco et al., 1990), and is considered a forerunner in acknowledging ethnic solutions for the care of patients in pain.

In 2002, a project on patients suffering from FMS was started in cooperation with Giovanni Biasi from the Rheumatology Clinic of Siena University. Carli introduced the Italian version of the Multidimensional Pain Scale (MPS), a pain questionnaire developed at Columbia University in New York where Carli had been a visiting professor in 1993. The MPS included the dimension of well-being in the profile of pain subjects. Surprisingly, many FMS patients self-rated high levels of well-being, in spite of their multi-locular pain that typically did not sufficiently respond to analgesic medication or other therapy. Thus Carli and his group (Anna Lisa Suman and Alexa Huber) started to consider well-being as a separate psychological dimension partially independent of the suffering of pain. They devised a multidisciplinary treatment programme based on cognitive behavioural therapy and aerobic physical training. Surprisingly, and against the predictions of many who had devised treatments for FMS previously, the results showed reduction of pain to tolerable levels (Suman et al., 2009). At the same time, analysis of blood monocytes showed increased expression of glucocorticoid receptors, suggesting improved function of the hypothalamic-pituitary-adrenal axis in countering pain mechanisms and experience. The treatment programme induced a persistent change in the self-concept and physical activity behaviour in most of the FMS patients involved in the programme.

Thus, the neurosciences owe an impressive contribution from Giancarlo Carli’s life work (www.giancarlocarli.com). The synopsis I have personally gained when preparing this laudation shows to me his great motivation and ability to unveil some of the secrets at the interface
between the subconscious and cognitive spheres of the brain and behaviour. His continued curiosity was obviously seeded 50 years ago as a beginner in neurophysiology and then shaped by the Moruzzi school of neuroscience. I have known Giancarlo personally for some 40 years, as a cultivated gentleman of classical education with a good sense of humour and, most importantly, as a reliable friend—thank you, Giancarlo!

REFERENCES


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NEUROIMAGING AND PAIN: IMPLICATIONS FOR PREVENTION AND TREATMENT

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ABSTRACT

This article reports our contribution to the meeting held in Siena in November 2010 in honour of Giancarlo Carli, who has worked extensively on animal and human models of pain and, in particular, on the cognitive dimensions of chronic pain. The paper deals with the brain changes related to acute and chronic pain in muscular and neuropathic pain patients. The long-term influence of perinatal pain on sensitization and pain processing is discussed as well as the influence of learning processes such as operant or classical conditioning. The review closes with implications for behavioural interventions.

Key words: brain changes, chronic pain, learning, preterm, sensitization, behavioural interventions

It was a pleasure for us to join the meeting held in Siena in honour of Giancarlo Carli on the occasion of his retirement. In fact, we share with him a deep interest in pain and, more specifically, in the environmental and individual factors possibly influencing the experience of chronic pain (Carli et al., 2002; Huber et al., 2007, 2008, 2009; Carli, Huber et al., 2008; Carli, Suman et al., 2008; Gabriel et al., 2010). This paper reports our contribution to the congress.

BRAIN CHANGES IN CHRONIC NEUROPATHIC AND MUSCULOSKELETAL PAIN

In persons with amputations it has been shown that the region of the somatosensory cortex that formerly received input from the now amputated limb reorganizes and subsequently processes input from neighbouring regions (e.g. Elbert et al., 1994; Yang et al., 1994; Flor et al., 1995; Price et al., 2006). These changes are mirrored in motor cortex (Cohen et al., 1991; Kew et al., 1994; Karl et al., 2001; Lotze et al., 2001; Karl, Muhlnickel et al., 2004). Interestingly, reorganizational changes were only found in amputees with phantom limb pain after amputation, but not in amputee patients without pain (Flor et al., 1995). This suggests that pain may contribute to the changes observed and that the persisting pain might also be a consequence of the plastic changes that occur. In several studies carried out on human upper-extremity amputee patients, displacement of the lip representation in the primary motor and somatosensory cortex was positively correlated with the intensity of phantom limb pain, and was not present in pain-free amputee patients or healthy control subjects (e.g. Flor et al., 1995; Diers et al., 2010). In addition, in the patients with phantom limb pain, but not in the pain-free amputee patients,
imagined movement of the phantom hand was shown to activate the neighbouring face area (Lotze et al., 2001). This co-activation probably occurs due to the high overlap of the hand, arm, and mouth representations.

Similar observations have been made in patients with complex regional pain syndrome (CRPS). In these patients, the representation of the affected hand tends to be smaller compared with that of the unaffected hand and the individual digit representations had moved closer together (Juottonen et al., 2002; Maihöfner et al., 2003, 2006; Schwenkreis et al., 2003; Pleger et al., 2005). The extent of the pathological change in the cortical representations correlated with the intensity of pain or motor dysfunction (Maihöfner et al., 2004, 2007; Pleger et al., 2005), but was additionally related to a degradation of sensibility in the affected hand. It was, however, unrelated to a loss of motor function (Maihöfner et al., 2007). It is so far not known how an expansion of adjacent representations and a shrinking of adjacent representations as observed in phantom limb pain and CRPS, respectively, can both be associated with pain. It is also not known to what extent nociceptive and non-nociceptive neurons interact in this process and how inhibitory and excitatory mechanisms influence each other.

Not only decreased input related to deafferentation but also increased behaviourally relevant input related to non-neuropathic pain leads to changes in the cortical map in chronic musculoskeletal pain syndromes such as chronic back pain (CBP) or fibromyalgia (FM) (Flor, Braun et al., 1997; Gracely et al., 2002; Giesecke et al., 2004; Tsao et al, 2008 Burgmer et al., 2009). For example, Flor, Braun et al. (1997) reported a close association between the chronicity of back pain and enhanced excitability and map expansion of the back representation in primary somatosensory cortex in patients with non-neuropathic back pain. The back representation had expanded and shifted towards the leg representation the longer the pain had persisted. This was site-specific since the hand representation was unaffected. Similar changes were reported by Giesecke et al. (2004) using functional magnetic resonance imaging. Recently, Tsao et al. (2008) observed a close interaction between changes in motor cortex and postural control in patients with CBP suggesting an intricate interaction between peripheral and central traces of plastic changes related to chronic pain.

Greatly enhanced representations of painful stimulation were also found in patients with fibromyalgia. Gracely et al. (2002) reported that comparable levels of subjectively reported painful stimulation resulted in cerebral activation patterns that were similar in FM patients and healthy controls. However, similar stimulation intensities resulted in stronger activation in regions specific for pain processing in FM patients, supporting the hypothesis of augmented pain processing in FM patients. Cook et al. (2004) examined painful heat stimuli (47°C) to the non-dominant thenar in patients with FM and healthy controls and observed activations in primary and secondary somatosensory cortex, the anterior cingulate cortex, the supplementary motor area, and the insular cortex. Contrasts between both groups revealed significantly more activation for the FM group in the contralateral insular cortex. For perceptually equivalent pain ratings FM patients failed to respond to pain provocation in the descending pain regulating system (the rostral anterior cingulate cortex) (Jensen et al., 2009).

These changes were present in cortical activation maps as well as in areas involved in the affective and cognitive processing of pain (Burgmer et al., 2009). Catastrophizing was found to be significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal anterior cingulate cortex, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala),
and motor control when depressive symptomatology was controlled for (Gracely et al., 2004). Symptoms of depression and the presence of major depressive disorder were associated with the magnitude of pain-evoked neuronal activations in brain regions associated with affective pain processing (the amygdalae and contralateral anterior insula cf., Giesecke et al., 2005). Patients with major depressive disorder show hyperalgesia, but the hyperalgesia is more pronounced in FM and a deficit in pain inhibition is specific to FM (de Souza et al., 2009; Normand et al., 2010). A recent study with 83 subjects showed that depressive symptoms, anxiety, and catastrophizing scores were correlated, but did not correlate with ratings of clinical pain or with sensitivity to pressure pain (Jensen et al., 2010). Brain activity during experimental pain was not modulated by depressive symptoms, anxiety, or catastrophizing (Jensen et al., 2010). The general and widespread nature of pain in FM suggests the involvement of central mechanisms via spinal and/or supraspinal modulation of experimental peripheral input. The exact interplay of pain, anxiety, depression, and catastrophizing needs to be further investigated and can be different in different subgroups of patients (Flor & Turk, 2011).

In addition to changes in functional activation, structural and biochemical changes and changes in brain connectivity have also been reported for musculoskeletal pain syndromes (e.g. Kuchinad et al., 2007; Schmidt-Wilcke et al., 2007; Staud & Spaeth, 2008). They might, however, be a consequence rather than a cause of the pain (Seifert & Maihöfner, 2011).

PRETERM SENSITIZATION

An especially interesting example of brain changes correlated to injury and stimulation related to pain are changes that occur as a consequence of painful stimulation early in life. Whereas formerly it was assumed that there is no pain perception in the neonate, more recent evidence shows not only that neonates perceive pain but that pain leads to long-lasting negative consequences (Thewissen & Allegaert, 2011). The neonatal period is a particularly sensitive time window for experience-induced neuronal plasticity due to the ongoing maturation of the nociceptive (Fitzgerald & Jennings, 1999) and the sensory systems (Berardi et al., 2000). In animal studies it has been shown that neonatal pain experiences can induce long-term hypoalgesia or hyperalgesia (Anand et al., 1999; Lidow, 2002). Similar findings have been obtained in humans. Twelve years after treatment in a neonatal intensive care unit both preterm and full-term children showed greater perceptual sensitization to tonic heat and elevated heat pain thresholds compared to control children without neonatal intensive care unit experience (Hermann et al., 2006). In response to tonic heat pain preterm children showed significantly higher activations in primary somatosensory cortex, anterior cingulate cortex, and insula compared to controls (Hohmeister et al., 2010). This suggests that repeated pain experience in neonates may induce activity-induced changes in the functioning of pain pathways that persist well beyond infancy.

A changed pain perception has also been observed in school-aged children who suffered during the age of 6–24 months from moderate or severe burn injuries. Moderately burned children had significantly higher mechanical detection thresholds and significantly lower mechanical pain thresholds and significantly greater perceptual sensitization to repetitive mechanical stimuli compared to controls (Wollgarten-Hadamek et al., 2009). Severely burned children had elevated heat pain thresholds and significantly greater perceptual sensitization to thermal stimuli compared to controls (Wollgarten-Hadamek et al., 2009). This suggests that early traumatic and painful injuries can induce global, long-term alterations in sensory and
pain processing also on body sites not affected by the burn injury. It is possible that sensitized excitatory pain pathways result in a disturbed endogenous pain inhibitory mechanism and can be tested with stress-induced analgesia, a reduced nociceptive response after stress exposure, which is mediated by descending inhibitory opioid and non-opioid brain circuits (Akil et al., 1976; Willer et al., 1981; Flor & Grüsser, 1999; Flor et al., 2002; Yilmaz et al., 2010). Moderately burned children and controls showed intact stress-induced analgesia whereas severely burned children failed to show significant stress-related changes (Wollgarten-Hadamek et al., 2011). In addition, in neonates brain regions involved in pain inhibition were underactivated whereas brain regions that reflect especially the affective component of pain were overactivated (Hohmeister et al., 2010). A counter-irritation-induced analgesia with a cold pressor pain stimulus reduced heat pain intensity ratings in term-born children and preterm children with few painful interventions at birth, but not in preterm children with numerous painful procedures during the neonatal period (Goffaux et al., 2008). This suggests that pain and stress exposure in neonates and infants may be associated with an attenuated stress-induced activation of endogenous pain inhibitory mechanisms later in childhood and adolescence.

LEARNING MECHANISMS IN CHRONIC PAIN AND SENSITIZATION

In addition to sensitization (a non-associative learning process), associative learning such as operant or Pavlovian conditioning can influence the processing of pain on all levels—the verbal-subjective, the behavioural, and the physiological (Fordyce, 1976; Linton & Gotestam, 1985; Flor & Turk, 2011). Fordyce (1976) proposed that positive as well as negative reinforcement of pain behaviours (such as sighing or grimacing) and a lack of positive reinforcement of healthy behaviours (such as movement or smiling) can increase the expression of pain behaviours and over time lead to behaviourally induced chronic pain problems. Direct verbal reinforcement of pain has been identified as an important modulator of the pain response. When patients and healthy controls were reinforced for increasing or decreasing their verbal pain responses both patients and controls learned this task equally well; however, the patients showed a delay in the extinction of the verbal pain response.

When somatosensory evoked potentials to the pain stimuli were examined, the late event-related responses (> 250 ms) were unaltered and showed mainly habituation. However, the early response (N150) was affected by the conditioning procedure and remained high in the chronic pain group that had been reinforced for higher pain ratings during extinction. This indicates a direct effect of verbal reinforcement on the early cortical processing of nociceptive information (Flor et al., 2002). This lack of extinction in cortical processing implies that maladaptive learnt physiological responses may greatly contribute to pain chronicity. Chronic pain patients might also have learned to increase muscle tension in anticipation of painful stimuli to reduce pain. This would result in negative reinforcement (because a negative consequence, pain, is eliminated) and could lead to short-term pain reduction, but on the long term stimulate and sensitize nociceptors and thus increase pain. During painful stimuli on the lower arm or back, chronic back pain patients were instructed to increase their muscle tension or keep it low. During the tension increase condition, the CBP patients but not the healthy controls showed higher N150 and N150/P260 amplitudes (Knost et al., 1999). Thus, operantly conditioned muscle tension could contribute to chronicity.
In a study in which pain was implicitly reinforced, a series of tonic painful heat stimuli were applied to the dominant hand. Patients had to adjust the temperature at the end of each trial to the subjective temperature felt at the beginning of each trial, which was objectively not changed. The temperature was increased or decreased in each subsequent trial, depending on the adjustment in the trial before. Thus the behaviour of the subjects was reinforced without their knowledge. It was shown that increased or decreased pain sensitivity could be implicitly learned (Hölzl et al., 2005). In another study sensitization could be modulated by implicit reinforcement (Becker et al., 2008). Thus, operant learning mechanisms based on intrinsic reinforcement may provide an explanation for the gradual development of sustained hypersensitivity during pain that is becoming chronic (Becker et al., 2008). Using this paradigm in patients with FM, one subgroup with and one without irritable bowel syndrome (IBS), it was shown that FM patients without IBS sensitized in the habituation learning condition. FM patients with IBS demonstrated neither learning of sensitization nor habituation. Thus, operant perceptual learning seems to be impaired in patients with FM (Becker et al., 2011).

Another type of learning that is important for pain modulation is Pavlovian conditioning where originally neutral stimuli become associated with pain and can later by themselves enhance pain perception and induce chronicity. In a typical aversive Pavlovian differential delay conditioning procedure, aversive pictures were paired with painful electric stimulation, whereas positive pictures were paired with the absence of shock (Schneider et al., 2004). Chronic back pain patients showed an enhanced muscular response of the left forearm (where the unconditioned stimulus was applied) to the reinforced conditioned stimulus already in the pre-conditioning phase indicative of more anticipatory anxiety towards the painful stimulus. During learning the painful muscle showed an increased response to the reinforced conditioned stimulus and an increased response to the reinforced and unreinforced conditioned stimulus in the extinction phase. These data were complemented by brain changes that were indicative of an altered anticipatory brain response as evidenced by the contingent negative variation that develops between the conditioned and the unconditioned stimulus.

Diesch and Flor (2007) showed that non-painful tactile stimulation can change the organization of the primary somatosensory cortex. Non-painful stimuli to the finger were used as conditioned stimuli and painful electrical stimuli to the back as unconditioned stimuli. This study in healthy controls showed that humans easily acquire a conditioned muscular response in this conditioning paradigm compared to an unconditioned control group where the stimuli were randomly distributed. The cortical representation of the conditioned finger increased and shifted in the direction of the back compared to the control finger. These data can be interpreted as reflecting the development of a cortical network that associates more and more formerly neutral stimuli into a 'pain network' that then triggers pain perception and behavioural pain responses. It should be noted that there is considerable overlap between the processing of pain and other negative emotions and that these networks interact (Legrain et al., 2011).

There is also indirect evidence of conditioning for pain-related words. Several studies found that painful words such as ‘burning’, ‘sticking’, and ‘pricking’ led to changed brain responses and hyper-reactivity in chronic pain patients compared to non-pain-related bodily sensations such as ‘sweating’ or ‘breathing’ or neutral words such as ‘walking’ or ‘standing’. The early component (N100–N150) of the event-related potential was increased for the pain-related words in both chronic and subchronic pain patients (Flor et al., 1997; Knost et al., 1997) and showed
increased blood-oxygen-level dependence in the left orbitofrontal cortex and anterior insula in migraine patients (Eck et al., 2011).

Another study showed that this effect can be induced in a learning process in healthy subjects. In a classical conditioning study pairing pseudo-words with painful electrical stimuli an increased N100 response, especially over the left hemisphere, was found after the conditioning procedure (Montoya et al., 1996). Thus chronic pain can lead to the development of a somatosensory memory for pain with changed maps in the somatosensory cortex and changes in other brain areas, as well as hyperalgesia in the absence of peripheral nociceptive stimuli. These processes lead to more attention to the formerly neutral stimuli because they increase their salience and attentional processes can further enhance the learning and brain changes (Rainville et al., 1997; Buchner et al., 1999; Valet et al., 2004). Learning and attentional processes thus cause additional and widespread implicit memory traces and reinforce the existing pain memory via connections with affective brain areas. In addition to local changes a general cortical excitability was found in chronic pain (e.g. Larbig et al., 1996; Karl, Diers et al., 2004).

BEHAVIOURAL INTERVENTIONS

The assumption that chronic pain is greatly influenced by learning and memory processes suggests that treatment should focus on the alteration of these memory traces. Behavioural and cognitive methods or their combination are especially well suited for this purpose because they can specifically alter the brain change that is prominent in a specific condition whereas pharmacological treatments act in a more unspecific manner. Patients who show high levels of pain behaviours and are much incapacitated by their pain should profit from operant behavioural treatment. The goals of this treatment are: the decrease of pain behaviours in an effort to extinguish pain; the increase of activity levels and healthy behaviours related to work, leisure time, and the family; medication reduction and management; and the change of the behaviour of significant others (Fordyce, 1976). The overall goal is to reduce disability by reducing pain and increasing healthy behaviours. Medication is switched from a pain contingent to a fixed time schedule, where medication is given at certain times of the day to avoid negative reinforcement learning. Similar principles are applied to the enhancement of activity, and the reduction of inactivity and invalidity. This approach has been found to be effective in patients with chronic back pain as well as other pain syndromes such as FM (Thieme et al., 2003, 2006) and is especially effective in reducing pain behaviours.

The cognitive-behavioural model of chronic pain emphasizes the role of cognitive, affective, and behavioural factors in the development and maintenance of chronic pain. The central tenet of this treatment is to reduce feelings of helplessness and uncontrollability, and to establish a sense of control over pain in patients. This is achieved by the modification of pain-eliciting and maintaining behaviours, cognitions, and emotions. The cognitive-behavioural approach teaches patients various techniques to effectively deal with episodes of pain. Pain-related cognitions are changed by cognitive restructuring and pain coping strategies, such as attention diversion and use of imagery or relaxation that increase self-efficacy. Several studies have examined the efficacy of cognitive-behavioural pain management, which must be considered as a very effective treatment of chronic pain (Hoffman et al., 2007). Whereas operant treatment reduces especially pain behaviours and also pain intensity, cognitive-behavioural therapy has a special effect on the affective and cognitive aspects of pain (Thieme et al., 2006). Since extinc-
tion is more difficult than acquisition, principles of extinction training need to be considered (Flor, 2009).

Previous studies have used hypnosis to differentially modulate the sensory or affective component of pain and have shown differential changes of the primary somatosensory cortex or the anterior cingulate, respectively (Rainville, Carrier et al., 1999; Rainville, Hofbauer et al., 1999). Several studies have shown that hypnosis also effectively influences pain in chronic conditions and that it produces sizeable pain reductions (Carli, Huber et al., 2008; Carli, Suman et al., 2008; Dufresne et al., 2010). For example, hypnosis improved pain intensity in multiple sclerosis as well as cognitive restructurung with the best effects for the combined treatment (Jensen et al., 2011). Hypnosis was shown to have effects on both cortical pain modulation (by attention) (Rainville, Carrier et al., 1999; Rainville, Hofbauer et al., 1999; Derbyshire et al., 2009) and spinal pain modulation (Kiernan et al., 1995; Danziger et al., 1998).

Treatments that combine pharmacological interventions with behavioural and cognitive-behavioural interventions might be even more effective. In anxiety disorders it has been shown that exposure with or without additional pharmacological intervention can alter brain processes related to stimuli that are relevant for the disorder. The partial NMDA receptor agonist D-cycloserine has been found to be effective in enhancing extinction of aversive memories and has been used as an effective adjunct to exposure treatment in several studies (Ressler et al., 2004; Hofmann et al., 2006). D-cycloserine has also been shown to reduce neuropathic pain by itself in an animal model of neuropathic pain (Millecamps et al., 2007). In addition, cannabinoids have been identified as important modulators of extinction (Marsicano et al., 2002; Wotjak, 2005) and might be interesting compounds to support extinction training. Since pain seems to generally increase excitability, substances that decrease excitation, such as gabapentin or pregabalin, would also seem indicated as enhancers of extinction. Since extinction is context-specific, training should include as many varied behaviours and environments as possible. The use of stress and pain episodes to train relapse prevention are important parts of this training. In addition, cognitive and emotional aspects of pain need to be targeted (Flor, 2009).

CONCLUSION
Recent scientific evidence has shown that chronic pain leads to changes in many brain regions. In particular the neonatal period is a sensitive time window for experience-induced neuronal plasticity due to the ongoing maturation of the pain system. As classical and operant conditioning procedures are involved in the development of chronic pain, cognitive-behavioural treatments are very effective.

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AN ADAPTIVE FRAMEWORK FOR PARTURITION AND PREDATION PAIN

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ABSTRACT

Two of the pain situations that have been studied by Giancarlo Carli are parturition pain and the pain that accompanies immobility responses to a predator attack. An adaptive approach to these situations makes predictions about the level of analgesia or hyperalgesia that should lead to dampened or exaggerated pain responses in different contexts. In primates, there is evidence for significant pain during parturition in the form of writhing, stretching, and grimacing, but most cases feature little or no vocalizations. The prevalence of nighttime births in human and non-human primates is thought to be in part an adaptation to reduce predation, a situation where loud vocalizations would be counter-productive. Immobility responses after a predatory attack should also feature dampened pain responses. In line with this prediction, opiate analgesia has been demonstrated in immobilized rabbits. Other examples of adaptive responses to pain are given from the recent literature, including resistance to scorpion venom in grasshopper mice and socially induced analgesia to biting flies in deer mice.

Key words: pain, adaptation, evolution, parturition, death feigning, tonic immobility

If plants, through the evolution of capsaicin and menthol, can manipulate the pain responses of animals, it is logical to suppose that animals, which have the advantage of a nervous system, should also be able to do so. Capsaicin stimulates the heat receptors of mammals (Caterina et al., 1997; but not of birds, Jordt & Julius, 2002) so that animals avoid the fruit that contains it, while menthol does the same thing for leaves by stimulating mammalian cold receptors (Bautista et al., 2007). In these cases, animal responses have evolved according to the interests of plants. In general, however, we might expect they would evolve according to the interests of the animal experiencing the discomfort and pain and against the interests of the animal causing it.

Adaptive approaches to the study of pain are an important addition to traditional neuroscience approaches (Amit & Galina, 1986; Kavaliers, 1988). Adaptive views seek to (1) identify situations where pain varies in natural settings, (2) pinpoint the mechanisms behind the variation using behavioural experiments in captivity, (3) identify the neural mechanisms of the variation, as well as (4) the genetic differences that underlie them. The behavioural paradigms used in these studies go beyond the standard lab protocols of tail pinching, foot heating, and subcutaneous formalin injection and aim for increased ecological validity. The best examples of this approach come from studies of resistance to scorpion toxins in grasshopper mice (Rowe
et al., 2011), as well as analgesia produced in deer mice by natural stressors such as exposure to predators (Kavaliers, 1990) or parasitized mates (Kavaliers & Colwell, 1995) or attacks from dominant conspecifics (Teskey & Kavaliers, 1991) and biting flies (Colwell & Kavaliers, 1992).

The adaptive approach can be used on many types of pain. Two of the pain situations that Giancarlo Carli has worked on during his long research career, parturition pain and the pain that accompanies immobility responses to a predator attack, have been addressed with an integration of methods from neuroscience and behavioural ecology. In this paper, I first review this work, on which I have collaborated, and then give a series of examples from the recent literature using the adaptive framework.

Viewed in adaptive terms, behavioural responses to predation and parturition pain should vary according to the advantages the animal might incur in either dampening or exaggerating the external manifestation of pain (Amit & Galina, 1986). As these behavioural responses are strongly determined by the internal sensations, genetics, and neurophysiology of pain, the predictions should also apply to these levels. For instance, vocalizations, jumping, and writhing are among the most obvious behavioural responses to painful situations in mammals. One can expect these responses to be modulated according to their context as well as their effect on others. This adaptive logic is similar to the one that has been applied to other prey defences, such as the stotting of gazelles (FitzGibbon & Fanshawe, 1988) and the tail flashing of deer (Caro et al., 1995), which varies as a predator pursuit deterrent according to context.

Injury resulting from a predator attack should lead to very different responses if the predator has a biting hold on its prey (the prey should jump and writhe), if the prey shows extensive bleeding from a life-threatening wound (double up), if the prey is alone versus close to kin (vocalize), or if the predator has moved away from its prey after immobilizing it (stay immobile). The simplest way to modulate these responses would be to change pain thresholds in the appropriate direction via either analgesia or hyperalgesia.

Parturition is also thought to be painful in many eutherian mammals, but presumably not in monotremes or marsupials, who respectively bear eggs and undeveloped foetuses. Because brain growth, contrary to that of the rest of the body, occurs to a large extent in the embryo, eutherian species selected for large brain size (simian primates, elephants, Carnivora, and Odontocete cetaceans) might have to deal with significant levels of parturition pain. A female giving birth is very vulnerable, but risks for her are likely to be very different if she is a small, frequently hunted primate like a vervet monkey or a large predatory mammal like a polar bear or a killer whale. Behavioural manifestations of parturition pain should logically follow these varying risks, as should internal mechanisms. For example, the vocalizations that normally accompany the levels of pain that are thought to be present during parturition may place some animals at much greater risk than others.

One intriguing feature of parturition on both human and non-human primates is the fact that it most often occurs at night (Jolly, 1972). One plausible function for nighttime delivery is that it decreases exposure of vulnerable females to predation. If darkness offers visual concealment and eating of the afterbirth contributes to olfactory concealment, it would make sense if the loud vocalizations that often accompany pain in other situations were inhibited during parturition. Lefebvre and Carli (1985, 1986) tested this idea with a review of all cases (88 individuals in 29 species, 13 in the field and 75 in captivity) they could find on primate parturition. Mild or severe discomfort, in the form of straining, stretching, arching, grimacing, writhing, shaking, doubling up, eye closure, and restlessness was reported in 69 cases. Silence and
moderate level vocalizations were reported in 21 and 43 cases, respectively. Loud vocalizations occurred in only 6 cases. The trends therefore suggest that, during primate parturition, visible pain responses are seldom accompanied by the loud cries manifested by animals in other situations (Carli & Monti, 1987). In contrast, injuries encountered during intraspecific aggression are accompanied by very loud screams (e.g. Yamada and Nakamichi, 2006, a juvenile bitten by an adult male). In rats, vocalizations that are emitted during attacks by dominants and electric shocks (van der Poel & Miczek, 1991) are absent during parturition, despite the presence of straining and stretching behaviours that are strongly reduced by epidural morphine (Cathe-line et al., 2006) and can thus be seen as symptoms of pain. In an intriguing follow-up on the known nighttime bias of births in humans, Harkness and Gijsbers (1989) report that stress and pain levels are lower for nighttime births than they are for daytime births. They suggest this might derive from the anti-predator advantage of nighttime parturition.

A similar situation might occur during immobility responses to a predator attack. Many prey species show a form of ‘death feigning’ when attacked by a predator, the most famous being the ‘playing possum’ shown by the Virginia opossum Didelphis marsupialis (Gabrielsen & Smith, 1985). The immobility is thought to minimize prey movement cues likely to stimulate predator attack. In the lab, the prey species most often studied are chicken, quail, and rabbits, and the predator attack is simulated by a human forcefully restraining the animal. The prey’s response is operationalized by the time it takes to right itself after ceasing to struggle, following the blocking of the normal righting reflex when the prey is maintained on its back. Researchers in physiology and comparative psychology have also called this response ‘animal hypnosis’ and ‘tonic immobility’. The duration of immobility varies according to many factors, but the fact that it is increased by experimental manipulations of fear (Gallup, 1977) and decreased by the habituation brought on by repeated elicitation (Lefebvre & Sabourin, 1977a, 1977b) are consistent with an interpretation based on passive predator avoidance. As further evidence for this function, Jöngren et al. (2010) have shown that measures of tonic immobility in red junglefowl load on the same principal components as responses to a ground predator (a moving stuffed pine marten), and to a lesser extent responses to an aerial predator (flying hawk model). Jöngren and colleagues (2010) have also identified 13 genetic loci that differ between individuals that show more versus less tonic immobility.

According to an adaptive framework, if the response most likely to lead to survival after an attack is writhing, jumping, and loud vocalization, so that the predator is startled and loses its grip, the most efficient mechanism to achieve this should be intense pain. If, on the contrary, the best response is immobility, a decrease in pain would be ideal. In line with this prediction, Carli and collaborators were the first to show that pain appears to be reduced during ‘death feigning’ (Carli, 1975; Carli et al., 1976, 1977) and that the mechanism for this reduction might be opiate analgesia (Carli et al., 1981; reviewed by Porro & Carli, 1988). These results have since been extended to other species (Leite-Panissi et al., 2001; Miranda et al., 2006) and progress has been made on identifying the mechanisms of both immobility and its accompanying analgesia (Menescal-de-Oliveira & Hoffmann, 1993).

The adaptive framework can also provide insights into other types of pain. For example, Weary and Fraser (1995) point out that adaptive variation in pain should be taken into account in interpreting the behaviours of stressed animals. Pigs, for instance, are well known for their loud cries when handled, a baseline against which the increased screams of males when castrated need to be titrated (Weary et al., 1998). Recent work by the Kavaliers and Mogil re-
search groups also suggests that social context plays a role in pain responses. Here, it is not so much the broadcasting of pain via loud vocalizations and writhing that appears to have been selected, but the ability of observers to detect pain in the social cues given off by conspecifics. These cues may not be deliberately broadcast (Danchin et al., 2004), but they are available to animals that observe them in others. Kavaliers and colleagues (2005) have shown that pre-exposure to biting flies leads to defensive burrowing and analgesia in both the bitten mouse and in familiar conspecifics that have witnessed either the biting or the subsequent defensive burrowing of the victim. Pain does not have to be broadcast by vocalizations, but can be picked up by observational information given by reliable facial (Langford et al., 2010) and postural (e.g. writhing; Langford et al., 2006) indicators of pain.

An elegant example of the way an adaptive framework to pain can integrate multiple levels of explanation is the work of Rowe and collaborators on resistance to scorpion toxins in grasshopper mice. Grasshopper mice (genus *Onychomys*) are predatory rodents that eat several kinds of insects, including scorpions. Young grasshopper mice show symptoms of pain when stung by *Centruroides* scorpions, but they improve their predatory skills with age and are resistant to the paralysing and often lethal effects that the scorpion venom has on other rodents (Rowe & Rowe, 2006, 2008). Grasshopper mouse resistance appears to be specific to *Centruroides* toxins: house mice respond much more strongly to scorpion venom than do grasshopper mice, but both show the same response to formalin injection (Rowe et al., 2011). The scorpion venom binds Na\textsubscript{v}1.7, a Na\textsuperscript{+} channel expressed in mammalian pain-sensing neurons; genetic studies have identified four amino acid substitutions at highly conserved positions in grasshopper mice Na\textsubscript{v}1.7 that differ from orthologs in other rodents (Rowe et al., 2011).

Studies of this type that identify the evolutionary ecology of a pain response, its behavioural characteristics, neurophysiological mechanisms, and genetic background are not only valuable for their intellectual elegance. A complete, integrative understanding of the way evolution has led to analgesia in a specialized case like the grasshopper mouse might yield general insights applicable to less specialized situations. Finding out how evolution has solved specific problems in a few species may save researchers a lot of work in figuring out the general rules that they can apply to other species, including humans.

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METHODS AND BASIC MECHANISMS: BUILDING UP MY MIND

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ABSTRACT

This report briefly runs through my intellectual and human experience with Professor Giancarlo Carli. My interaction with him has allowed me to practise the scientific method of analysis and synthesis. It also enabled me to become aware of the potency and high inclusiveness of basic mechanisms in physiology (and pathology). Both these aspects produced many positive results: scientific publications and a far more advantageous way to face my clinical activity in a neonatal intensive care unit.

Key words: methods, Descartes, basic science, pain, psychometry, placebo

The breaking up of events that we observe in constituent dimensions, the analysis of the dimensions we have inferred and their subsequent reduction into a single, unifying concept; this is one of the first notions on scientific method that left a lasting trace on me during my early studies (Anonymous, 1637). And also the subtle, intellectual pleasure experienced on enquiring whether, in a given context, δεινόσι means terrible or excellent, and finally the search for a clue some time later that allowed me to opt for one of the possible translations. Another deep-rooted inheritance from my early studies was the reassuring certainty that every context contains within it the marks of the underlying truth as well as the sense of well-being that results from having resolved the anxiety of doubt.

Prompted by these thoughts and sentiments, and after several years of anaesthesiologic technique—in which the mind is suppressed and only the brain remains with minimal biological processes—I broke down what I observed every day and, as an anaesthesiologist, contributed to produce: the pain of patients who had undergone thoracotomy. These patients resorted to multiple cognitive structures and internally generated means to modulate, control, and sometimes reduce pain. I deconstructed the phenomenon, interpreted, analysed and then recorded the facts.

It was against this background that I met Professor Carli who taught physiology at the School of Medical Psychology at the University of Siena where I had enrolled in an attempt to expand my cultural horizons. Together we shared the material, gave a name and a cultural collocation to the mechanisms I had perceived, and verified them through rigorous statistical analysis. During this collaboration, he behaved as an understanding mentor—abstract in the evanescent and powerful labyrinths of curiosity; concrete in the
constructive realms of science. And, thus, pain became the ultimate outcome of the interaction between the nociceptive system of each patient and instructions and setting (Bachiocco et al., 1990), self-control expectancy (Bachiocco, Morselli et al., 1993), direct and vicarious learning (Bachiocco, Scesi et al., 1993), coping resources (Bachiocco et al., 1994; Bachiocco & Carli 1996), sleep and dreaming (Bachiocco et al., 1987); these also being means of coping, although in a completely unconscious way. In other words, pain became the activation of the prefrontal cortex and the descending inhibitory system (Basbaum & Fields, 1984) which produces an endogenous analgesia, but also of the high order occipito-temporal visual cortex, which is the substrate of vivid visual imaging during dreams (Nir & Tononi, 2010). And perhaps, in some cases and at some moments (we hope not), nociception became hyperalgesia from sleep loss (Roehrs et al., 2006) and activation of the descending facilitatory pathways (Porreca et al., 2002) from unsuppressed peripheral nociceptive input.

This evenience is not provable, but this was, nevertheless, the long-standing protocol applied at that time in our department of thoracic surgery (Bachiocco et al., 1990). The need to identify objective tools in order to assess the cognitive dimensions that modulated pain in each patient led us to study the basic properties and statistics of psychometry. The questionnaires administered to the patients became small tools that were, step by step, confirmed and validated by the material I had collected. This lengthy work made us aware that the armamentarium of psychometric tests available in Italian clinics lacked many tools for the assessment of pain and of pain patients. This conclusion motivated the project with Professor Clark to translate and validate the Multidisciplinary Affect and Pain Survey (Carli et al., 1997) that was started, and then continued, by the researchers of the Physiology Department.

Far more important were the results obtained when I translated and applied in clinics this method —by now well tried and tested—of analysing and synthesizing the event of interest (cognitive or biological) and comparing what we have inferred with what is already known. Furthermore, the recourse to basic science enabled me to realize the potency and high inclusiveness of basic mechanisms, since nature is ultimately parsimonious.

For many years, I worked in a newborns and paediatric intensive care unit. In neonates, errors in the early stages of molecular pathways or anatomical structure development—still enormously plastic—give rise to a variety of malformations or dysfunctions which, in many cases, still lack definitions, nosological labels, and suggestions for management. So, the case series reports and the systematic reviews published in the literature are poor or completely absent, and diagnosis and treatment is a tremendous challenge. In such cases, investigating signs and symptoms with the most advanced techniques, and clustering them under a few or a single mechanism taken from basic science, may be determining and change the outcome. This step must be followed by a constant bidirectional approach between the bedside and the bench which has inspired the interpretation.

The long training on methods and basic science from which I benefitted from Professor Carli is, I think, one of the main sources of the sense of mastery that I have often felt in such, sometimes hard, contingencies. My knowledge of pain and psychometry produced specific fruits. I thus built up a pain programme to educate nurses and medical personnel in my hospital (Bachiocco et al., 2005), and the protocols to manage and monitor pain in neonates and children in my department (Bachiocco, Pigna, et al., 2007). I also took into consideration a model to explain the gain of the withdrawal syndrome presented by neonates when hypoxic (Bachiocco et al., 2006) and felt the need to objectify, by means of psychophysics, the so-
matosensory sensitivity/insensitivity of a girl clinically diagnosed with HSAN IV (Bachiocco, Bergamaschi et al., 2007). Moreover, I searched for the expression of some genes likely to be involved in this disorder (Bachiocco et al., 2011). The case of Julia has deep roots (Bachiocco & Mondardini, 2010). It was naturalistic evidence that I discerned by virtue of my studies on learning through conditioning and on anticipation through expectancy. Thus, while the baby was building up a placebo response, I became increasingly convinced that she was doing just this. So, when I perceived that the infant’s response was fully developed, I didn’t administer drugs. But on this matter, the mentors were many and all excellent (Tiengo et al., 1994).

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Acknowledgements: The most important thought that comes to mind in briefly reviewing this intellectual and human experience is that my interaction with Professor Carli has allowed me to exercise with lightness and fun a part of my mind that would otherwise never have emerged, or else emerged but with a far greater effort.
PSYCHOLOGICAL ASSESSMENT OF MIGRAINE AND OTHER HEADACHES AND NOVEL PREVENTIVE POTENTIAL OF A SOCIAL NETWORK

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ABSTRACT

In patients with different headache types the prevalence of behavioural and somatic symptoms and its relation to the patients’ personality and psychiatric comorbidity were investigated. The data showed that: (1) the symptom prevalence is significantly higher in patients with migraine and tension-type headache than in headache-free controls; (2) distinctive personality traits are observed in patients with chronic headache; and (3) among these patients psychiatric comorbidity is elevated and is associated with an increased burden of symptoms. In a study in which a psychological assessment and muscle palpation of craniocervical muscles were carried out in headache patients it was found that anxiety and depression considerably increased the level of muscle tenderness. In an eight-month controlled trial conducted to evaluate the effectiveness of an educational and physical programme designed to decrease muscle tension it was found that subjects in the study group reported more than a 40% reduction in headache and myogenous pain. Following these results we have launched a social network (www.noheadneckpain.com) to prevent and reduce headache, shoulder, and neck pain in an extensive population. Here everybody has free access to the educational and physical programme. In a reserved section clinicians have access to regularly updated educational and scientific material.

Keywords: headache, migraine, personality, psychosomatic symptoms, psychiatric comorbidity

Different approaches may be employed to examine the psychological aspects of patients with migraine and other headache types. Headache patients often report the presence of psychic, behavioural, and somatic symptoms (Mongini et al., 1997). This issue also relates to the problem of whether an association exists between personality changes, psychiatric disorders, and the different headache types. Thus, the assessment of the prevalence of such symptoms in a population of headache patients may be of help in evaluating the psychogenic component in these patients. Personality traits in headache patients may also be assessed by means of different psychometric tests. Among them, the Minnesota Multiple Personality Inventory is one of the most widely used instruments to assess personality factors in patients with different headache types (Kudrow & Sutkus, 1979; Sternbach et al., 1980; Andrasik et al., 1982; Ellertsen & Klöve, 1987; Pfaffenrath et al., 1991; Mongini et al., 1992, 1994, 2000). The association between migraine and psychiatric disorders has long been investigated through
Figure 1. The two patient clusters obtained after K-means cluster analysis show significant differences in the percentage prevalence of psychosomatic symptoms.

Source: Modified from Mongini et al., 2002.
epidemiological and prospective studies (Merikangas et al., 1988, 1993; Marchesi et al., 1989; Brandt et al., 1990; Breslau & Davis, 1993; Breslau et al., 1994, 2000, 2003; Silberstein et al., 1995; Guidetti et al., 1998; Cassidy et al., 2003; Hamelsky & Lipton, 2006; Victor et al., 2010).

This paper reports some personal contributions to these issues. They were a matter of exchange of ideas and debate with Professor Giancarlo Carli and were also presented in some of the meetings that he organized. Giancarlo’s interest, attention, and pertinent observations have been particularly encouraging and helpful for my work. Thank you Giancarlo for your continuing friendship and support.

HEADACHE, PSYCHOSOMATIC SYMPTOMS, AND PERSONALITY TRAITS

Patients suffering from headache usually complain of numerous accompanying psychic, behavioural, and somatic symptoms. To assess the prevalence of a number of such symptoms in migraine patients and to investigate if they are related to the patient’s personality, 53 women with migraine were enrolled and record was taken of 26 symptoms, behavioural or somatic. These symptoms had been found to be significantly different in groups of healthy subjects and patients with systemic or psychological disorders, respectively (Mongini et al., 1993). The Minnesota Multiphasic Personality Inventory (MMPI) and the Spielberg State and Trait Anxiety Inventory (STAI) were also administered (Mongini et al., 2002). The data relating to the accompanying symptoms were then processed through a self-organizing map (SOM) system; that is, a technique of artificial intelligence by which a large amount of data can be managed using a neural network model (Kohonen, 1995).

Since two clusters were identified by SOM analysis, K-means cluster analysis was further employed. This procedure identifies relatively homogeneous groups of cases based on selected characteristics by means of an algorithm that can handle large numbers of cases but requires the number of clusters be specified (Tryon & Bailey, 1973). Thus, in our case, two patient clusters were obtained showing a significant difference in prevalence of the majority of the symptoms examined (Figure 1).

The MMPI profile of the two patient clusters (Figure 2) was normal for the cluster with low prevalence of psychosomatic symptoms while the cluster with high prevalence of symptoms showed a consistent elevation of several MMPI scales. Also the data of the STAI showed a significant difference between the clusters.

It was concluded that the presence of behavioural symptoms in women with migraine may allow a distinction between two patient categories, with low or high scores of symptoms respectively. This difference does not seem related to the headache characteristics but, rather, to the patient’s personality.

More recently, the prevalence of accompanying symptoms in 506 patients with migraine and tension-type headache (both episodic and chronic) was compared to that in normal controls (Mongini et al., 2006). The results demonstrated an overwhelmingly higher number of accompanying symptoms in patients with migraine and tension-type headache (both episodic and chronic) than in headache-free controls. Psychiatric comorbidity was generally elevated. In particular, a significantly higher prevalence of psychiatric comorbidity was observed in chronic forms of headache with respect to episodic ones, most especially in patients with chronic migraine. The findings confirm that, in headache patients, psychiatric comorbidity is strictly associated with an increased burden of accompanying symptoms.
Figure 2. The two patient clusters with low (black) and high (white) prevalence of psychosomatic symptoms show significant differences of MMPI scales and STAI1 and STAI2 anxiety scores.

To examine the association between personality traits, depression, and migraine in the long term in 56 women with migraine, a psychological assessment was carried out to assess the presence of major depression, and the MMPI and the STAI were administered at baseline (T0) and after six to seven years (T2). Frequency, severity, and duration of migraine were recorded at T0, after treatment (T1), and at T2, and their association to the prevalence of depression and to the MMPI and STAI data was examined (Figure 3). Pain parameters improved in all patients in T0–T1. At T2, 32 patients had improved and 24 patients had not. At T0, the two groups had similar pain parameters. At T0, major depression was present in 37.5% of the patients who were improved at T2 and in 79.1% of those not improved.

Moreover, the patients whose migraine improved at T2 had significantly lower MMPI and STAI scores at T0 and T2. A comparative analysis of the data in the three periods considered seems to indicate that the relationship between pain frequency and severity and depression in migraine patients is bidirectional. The co-occurrence of depression and personality changes in women with migraine does not appear to influence the results of treatment at short term, but it seems to be influential on the headache history in the long term (Mongini et al., 2003).
PSYCHIATRIC COMORBIDITY AND MUSCLE CONTRACTION IN HEADACHE PATIENTS

While it is generally agreed that muscular factors are important in tension-type headache some data suggest that muscle tenderness could also be involved in migraine patients. It is therefore important to evaluate whether and how in migraine and tension-type headache muscle tenderness relates to anxiety and depression.

To this purpose in 459 patients with episodic migraine (EM), chronic migraine (CM), episodic tension-type headache (ETTH), chronic tension-type headache (CTTH), and EM+ETTH, a psychological assessment and muscle palpation of pericranial and cervical muscles were carried out. A muscle tenderness score was calculated (range 0–3). After logistic and linear regression analyses, anxiety and, to a greater extent, anxiety and depression combined, were positively associated to the muscle tenderness score in EM patients and in patients with EM+ETTH (Figure 4). We concluded that in patients with EM, the presence of anxiety or anxiety and depression combined considerably increases the level of muscle tenderness in the head and neck (Mongini et al., 2004).
The muscle tenderness score of pericranial and cervical muscles in patients with episodic migraine (EM) alone or in association with episodic tension-type headache (ETTH) significantly increases in presence of psychiatric comorbidity.

The more elevated muscle tenderness in migraine patients with psychiatric disorders might be one of the factors by which such disorders may influence the history of migraine and facilitate its evolution into CM. In a clinical perspective, it seems that in migraine patients both factors—muscle tenderness at palpation and the presence of psychiatric disorders—should be carefully investigated.

Muscle disorder, also defined as muscle hyper-parafunction, is a frequent condition in the craniofacial, neck, and shoulder areas and is considered a potential etiologic factor in some types of head pain. It includes tooth clenching, bruxism, tongue thrust, nail or lip biting, sustained contraction of the craniofacial and cervical muscles, and so on. Such muscle disorders may significantly increase muscle tenderness at palpation. Therefore, it is important to abate parafunctional habits in patients with headache of any type. We have for a long time been using a simple educational and physical programme designed to decrease muscle tension in the head, neck, and shoulder area. The programme consists of brief shoulder and neck exercises to be performed several times a day, a relaxation exercise, and instructions on how to reduce parafunction and hyperfunction of the craniofacial and neck muscles during the day.

An eight-month controlled trial (Mongini et al., 2008) was conducted to evaluate the effectiveness of this programme in reducing headache and myogenous pain (MP) originating in the neck and shoulder area. In the intention-to-treat population (n = 384), the authors found that at the baseline 70.2% of the subjects with pain had MP in the neck and shoulders associated with headache (TTH and/or M), while only 18.2% had headache without MP and 11.5% had MP without headache.

The follow-up data showed that subjects in the study group reported more than a 40% reduction in frequency of headache (Figure 5) and MP. The subgroup analysis showed that the
benefit was much greater in the subjects with both headache and MP. A significant benefit was found for patients with TTH with M, and TTH and M associated.

Figure 5. Reduction in headache frequency in the intention-to-treat population of a trial to evaluate the effectiveness of a workplace educational and physical programme. Results expressed as adjusted odds ratio (OR) (95% confidence interval). The vertical dashed line indicates the point where the study group began to follow the programme after a two-month baseline period. The number of subjects evaluated each month is indicated. Source: Modified from Mongini et al., 2008.

These results were confirmed at 12-month follow-up (Mongini et al., 2009). Furthermore, the follow-up data showed a consistent reduction in prevalence of accompanying symptoms in the study population (Rota et al., 2011).

CONCLUSIONS

In patients with chronic headache and cranio-cervical-facial pain, two comorbidities are frequently present: the psychiatric comorbidity and an excessive contraction of the cranio-cervical-facial muscles as a consequence of what is defined as muscle hyper-parafunction (Mongini et al., 2004).

While psychiatric comorbidity is frequently but not always considered, the second comorbidity, which is equally important, is often ignored. There is a strict relationship between the two since, as mentioned, they may reciprocally enhance one another.

In headache patients these disorders should be treated with a wide-ranging approach through extended data collection and clinical examination.
Psychiatric comorbidity, when present, is treated with relevant pharmacological and non-pharmacological therapy. As far as muscle hyper-parafunction is concerned, we apply, as mentioned, a simple cognitive and physical programme. The cognitive aspect of the programme aims to make the patient aware of his or her tendency to keep the muscles in a sustained state of contraction. To this purpose, we illustrate a simple relaxation exercise and suggest the use of visual reminders placed at strategic sites in the workplace and home. Furthermore, we have chosen three simple and efficacious exercises designed to recondition the muscles of the head, neck, and shoulders.

The research data support our clinical experience, confirming that the programme can be applied also for preventive purposes to all subjects with headache and neck pain in conjunction with the relevant pharmacological treatment. The programme may also be applied to large populations for preventive purposes. In this regard we have recently launched a social network (www.noheadneckpain.com) specifically designed to prevent and reduce headache, shoulder, and neck pain in an extensive population (Figure 6). Through the social network everybody has free access to the same programme that has already proven to be successful for a great number of individuals. It is possible to watch demonstration videos and download material with pertinent text and illustrations. The network is constantly updated with new information and initiatives. Visitors can interact with the network, describing their problems and asking questions.

Figure 6. The home page of the social network against headache and cervical pain.
In a reserved section, clinicians may look at the material provided, express their opinions, participate in debates, and present their own clinical and research data. They will also have access to the accumulated educational and scientific material that will be regularly updated on the site.

It is hoped that this initiative may represent a step forward in the daily struggle for the prevention and abatement of headache and craniocervical pain.

REFERENCES


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ONCE UPON A TIME: A RETROSPECTIVE OF NEUROENDOCRINOLGY OF ANIMAL HYPNOSIS IN THE RABBIT

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ABSTRACT

In immobility by inversion and restriction (animal hypnosis), studied in Carli’s lab in male rabbits in the late 1970s, the response to induction (the eliciting stimulus, regarded as an aversive event) was dissociated from response to hypnosis in terms of neuroendocrine systems activated and their time courses. Peripheral modifications of corticosterone (C) and testosterone (T), typical of the stress-response, were found following induction, not followed by immobility, with a marked and long-lasting increase in C (until 15 minutes after the end of the episode) and a parallel reduction of T. When induction was followed by immobility, there was a recovery of both hormones to control levels within 15 minutes. Hypnosis seems therefore to function as a sort of buffer – a compensation system re-establishing the previous endocrine balance with respect to a stressful event. This interpretation is supported by electrophysiological data, such as electroencephalography synchronization during hypnosis.

This recovery effect was present also in the adrenals, where the metabolites of the biosynthesis path of corticosteroids and of the adrenal androgens were modified in parallel to plasma alterations. In the anterior hypothalamus, hypnosis had no recovery effect on the depression of T metabolism, the latter being related to the neural circuits controlling sexual behaviour.

Key words: animal hypnosis, pituitary–adrenal system, pituitary–gonadal system, susceptibility, habituation

When I first met Giancarlo Carli, in the late 1970s, I was fascinated by his studies on animal hypnosis. Retrospectively, this was in fact the beginning of my interest in animal behaviour and its biological basis, which I developed later in my research.

Theoretical problems were raised by animal hypnosis at the time: in particular, whether or not the different immobility responses in various species—described with different names—refer to distinct phenomena or are the same phenomenon in different forms (the unitary explanation) (Lefebvre & Sabourin, 1977).

Experimentally, immobility by inversion and restriction of the animal was the most studied at various levels (e.g. stimulus, responses, physiological correlates); presented frequently at different evolutionary levels, it shows strong similarities in many species (homology). The model selected in Carli’s lab was immobility by inversion and restriction in the male rabbit—a docile animal with a high susceptibility to this response and suitable for neurophysiological studies.
A relevant contribution was given by Carli’s work on the neural control mechanisms (i.e. the localization of the neural centres necessary for the elicitation of the response) and the neurophysiological correlates of immobility response: in particular, the high voltage slow-wave pattern of electroencephalography (EEG) (synchronization) developed during the immobility response, alongside depression of reflexes and decreased muscle tone.

The subsequent step was to extend the study to the neuroendocrine correlates of animal hypnosis. These were the years of great development in the field of behavioural endocrinology, with fundamental findings in sexual differentiation and reproductive behaviour but also in the neuroendocrinology of responses to stress. The collaboration with Giancarlo Carli—and the beginning of a life-long friendship—was the result of the interests of a small group of people, including myself, to apply the rationale and methodologies of behavioural neuroendocrinology to animal hypnosis.

If the immobility response may functionally represent an extreme form of defence, the induction procedure—physical restraint in our case—can be regarded as an aversive, stressful event (Carli, 1982). Since the two components of induction and hypnosis are methodologically intertwined, our preliminary interest was to dissociate the response to induction (the eliciting stimulus) from hypnosis, in terms of neuroendocrine system activation and their time courses.

The question addressed was if and how hormones are influenced or influence this behaviour, by analyzing hormones (a) as correlates of susceptibility to immobility and (b) as modifications following immobility (effects).

The differences in susceptibility to hypnosis can be regarded as an example of the individual differences in the responses to environmental perturbations. This individual variability, hard to explain when interpreting experimental data, is in fact an opportunity to discover a variety of different mechanisms and strategies; this is the reason why studies of subsets of animals developed in various research fields, such as dominance/subordination, stress-responses, and anxiety profiles.

In animals, susceptibility to hypnosis is assessed through the mean duration of the episodes. Two subpopulations of animals can be distinguished: susceptible (SUS) and unsusceptible (UNS).

We selected two endocrine systems which are involved in adaptive responses and are sensitive to environmental stimuli, in particular to stress:


In our research, we developed different protocols, according to the aim of study (see Table 1).

**HYPNOSIS AND THE PITUITARY–ADRENAL SYSTEM**

*Corticosterone and susceptibility.* Corticosterone is the final step in the hormonal cascade of the pituitary–adrenal system, the main glucocorticoid secreted by cortical adrenals in rodents (cortisol is secreted in humans).
Table 1. Protocols developed in the reported experiments

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Treatment</th>
<th>Criteria/Time Course</th>
<th>Hormones/Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>5 trials/day 2 consecutive days</td>
<td>SUS: hypnosis duration &gt; 45 sec</td>
<td>Plasma basal levels C before treatment</td>
</tr>
<tr>
<td>(b)</td>
<td>Single block, 4 trials/1 day matched groups: IND/HYP</td>
<td>Longitudinal effects: 0, 15, 30 min</td>
<td>Plasma C, ACTH, beta-EP: repeated measures before/after treatment adrenal metabolites</td>
</tr>
<tr>
<td>(c)</td>
<td>Single episode matched groups: IND/HYP</td>
<td>Effects after 15 min</td>
<td>Plasma T; T, hypothalamic metabolites</td>
</tr>
<tr>
<td>(d)</td>
<td>5 trials/day until habituation</td>
<td>Habituation: hypnosis duration &lt; 45 sec, in 2 consecutive days</td>
<td>ACTH, T: plasma levels every day before treatment T hypothalamic metabolites</td>
</tr>
</tbody>
</table>

The correlation between corticosterone basal plasma levels (measured 24 hours before the treatment) and susceptibility to hypnosis has been proved in the experimental model of five trials per day for two consecutive days (Table 1(a)). Subjects were considered susceptible when the mean duration in the ten trials was above 30 seconds and the duration of the first episode was above 0 (with a positive correlation between the two criteria) (Carli et al., 1979).

Significant differences in basal C levels were found, with higher levels in SUS animals than in UNS, possibly indicative of a higher reactivity of the pituitary–adrenal system.

*Effects of induction and hypnosis on the pituitary–adrenal system.* A longitudinal protocol was developed to discriminate the effects of immobility from induction (IND) on pituitary–adrenal hormones, with their temporal pattern. The model (Table 1(b))—a single block of four trials during one day—included:

- Three immobility groups sacrificed at 0, 15, and 30 minutes after the last episode.
- Three induction groups: two groups sacrificed at 0 and 15 minutes, matched with immobility groups, with a period of time (empty time (ET)) after induction corresponding to the duration of hypnosis. Thus, the period between induction and sacrifice was the same in both the induction and the immobility groups.
- An additional group (00), sacrificed just after induction, represented the direct, immediate effect of induction per se, and the starting point of all other groups.

Corticosterone (C), adrenocorticotropic hormone (ACTH) and beta-endorphin were measured in plasma before the treatment (basal levels 24 hours before) and after the treatment at different times. Repeated measures were therefore available for each individual (before/after) (Farabollini et al., 1990).
Table 2 describes the hormonal modifications in both axes, following immobility and induction, starting from the first event in all groups (i.e. induction, group 00).

Table 2. Glucocorticoids and androgens modifications following immobility and induction

<table>
<thead>
<tr>
<th></th>
<th>Glucocorticoids</th>
<th>Androgens</th>
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<tbody>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction 00</td>
<td>C ↑↑; ACTH ↑</td>
<td></td>
</tr>
<tr>
<td>IND + HYP + 0</td>
<td>C =; ACTH ↑</td>
<td></td>
</tr>
<tr>
<td>IND + ET + 0</td>
<td>C ↑↑; ACTH =</td>
<td></td>
</tr>
<tr>
<td>IND + HYP + 15</td>
<td>C =; ACTH ↑</td>
<td>T =</td>
</tr>
<tr>
<td>IND + ET + 15</td>
<td>C ↑↑; ACTH =</td>
<td>T ↓ ↓</td>
</tr>
<tr>
<td>IND + HYP + 30</td>
<td>C ↑; ACTH ↑</td>
<td></td>
</tr>
<tr>
<td>Adrenal metabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction 00</td>
<td>C ↑↑; DOC =</td>
<td>T =; A =; 17a-OH-P=</td>
</tr>
<tr>
<td>IND + HYP + 0</td>
<td>C =; DOC =</td>
<td>T =; A ↑; 17a-OH-P=</td>
</tr>
<tr>
<td>IND + ET + 0</td>
<td>C ↑↑; DOC =</td>
<td>T ↓; A ↑; 17a-OH-P ↓</td>
</tr>
<tr>
<td>IND + HYP + 15</td>
<td>C =; DOC =</td>
<td>T =; A =; 17a-OH-P=</td>
</tr>
<tr>
<td>IND + ET + 15</td>
<td>C =; DOC ↑</td>
<td>T =; A =; 17a-OH-P ↓</td>
</tr>
<tr>
<td>IND + HYP + 30</td>
<td>C ↑; DOC =</td>
<td>T =; A =; 17a-OH-P=</td>
</tr>
</tbody>
</table>

Note: ↑↑ individual (before/after) significant differences; ↑ slight significant differences vs. control; = not modified. The methodological characteristics of this study were: (a) a longitudinal study with subsequent time points; (b) repeated measures available for each individual (before/after); (c) groups 0 and 15 for both (IND + ET) and (IND + HYP) directly comparable, the period between induction and sacrifice being the same; (d) a starting point, i.e. the first event in all groups, represented by the group (00).

In plasma, C was mainly affected by induction; after an early increase, just after induction (group 00), a long-lasting effect and potentiation was found in groups (0) and (15). There was no recovery during the ET following induction.

When induction was followed by hypnosis, no significant difference was found in the corresponding (0) and (15) groups; this was indicative of a recovery during hypnosis, with respect to the effect of induction.

As for ACTH, after a slight increase just after induction (00), no difference was found in the (0) and (15) groups.

When induction was followed by hypnosis, significant increments, with a rapid onset (0) and long-lasting effects (groups 15, 30) were found. In parallel, there was an overall slight increase of plasma beta-endorphin in the immobility groups, significant only in group 15. ACTH and beta-endorphin are released from the common precursor, proopiomelanocortin, in the anterior pituitary; these modifications are congruent with the activation of an opioid mechanism in the immobility response, as found in pain studies (Carli, 1982).

On the whole, different effects of immobility and induction were found, with a dissociation on C and ACTH.

The marked increase of C after induction, with early onset and long-lasting effects, indicates the activation of adrenals after induction (in the presence of a slight increment of ACTH).
When induction was followed by immobility, there was a recovery in C levels, in the presence of a consistent, rapid, and long-lasting increment of ACTH.

On the basis of these findings, we considered the possibility that responsiveness of adrenals could be differently affected by induction and hypnosis.

Adrenal metabolism was therefore studied in vitro, using progesterone (P) as substrate (Lodi & Lupo, 1990) in the longitudinal model (Table 1(b)). In the adrenal gland, P is a common precursor of the corticosteroids biosynthesis and of adrenal androgens: the metabolites of the biosynthesis path of corticosteroids measured were C and 11-deoxycorticosterone (DOC).

In the induction groups, C biosynthesis increased in the first steps (00, 0), with a slight increase of the precursor DOC only at time 15. In the immobility groups, the lack of effects on the metabolites was indicative of a recovery towards normal values due to hypnosis.

The effects of induction and hypnosis on adrenal metabolism were in the same direction of plasma effects, proving the involvement of the peripheral component of the stress axis in these events.

HYPNOSIS AND PITUITARY–GONADAL SYSTEM

The effects of the two components of the treatment—immobility and induction—on testosterone (T) plasma levels were studied following a single episode, with samples taken 15 minutes after the end of the episode (Table 1(c)). Animals of the induction group were matched with the immobility group, with a period of time (ET) corresponding to duration of hypnosis, so that the delay from induction to decapitation was the same in the two groups (Farabollini et al., 1978).

The effect of induction was a decrease in T levels after 15 minutes, an expected effect in the frame of the stress-response described in the literature. No effect was found after immobility (see Table 2). Hypnosis, as in the case of corticosterone and its adrenal metabolites therefore induced a recovery to control levels, antagonizing the effect of induction.

T levels in plasma depend upon peripheral endocrine activity of gonads and adrenals, but also upon central control on the other end of the axis (i.e. anterior hypothalamus). In the hypothalamus, neural circuits controlling sexual behaviour are activated by T; however, just in those years the aromatization hypothesis was formulated indicating that in mammals the conversion of T to estradiol (E) through aromatization is a necessary step for the expression of male sexual behaviour (McEwen & Krey, 1984).

Adrenal metabolism was studied in vitro, using progesterone as substrate, in the longitudinal model (Table 1(b)), measuring the main metabolites of the biosynthesis path of adrenal androgens at different times after the last episode: 17-α-hydroxyprogesterone (17-alfa-OH-P), androstenedione (A) and T (Lodi & Lupo, 1990).

In the induction group (see Table 2), biosynthesis of T was reduced at time 0 with recovery after 15 minutes; the same pattern was found for 17-alfa-OH-P (the first metabolite of P, precursor of A and T), reduced at time 0 and 15 minutes later.

The effect of induction on androgen metabolites was in the same direction as plasma effects, with a transitory reduction followed by a rapid recovery after 15 minutes, and in an opposite direction with respect to that on corticosteroids.
The lack of effects of hypnosis on T and 17-alfa-OH-P was indicative of a recovery towards normal values, proving also in this case a mechanism of compensation of hypnosis with respect to induction.

Androstenedione was slightly increased both after induction and immobility at time (0), with a recovery after 15 minutes; the pattern was the same of plasma levels—increased at time (0) with a recovery at 15 minutes (not shown in Table 2).

A dissociation between induction and immobility, with hypnosis re-establishing the pre-induction balance, is therefore present in the case of adrenal androgenic metabolites (i.e. on a peripheral target organ).

**Brain metabolism.** The brain can be regarded as a steroid hormones target tissue for the activation of behaviour, in particular sexual behaviour. We studied the metabolism of T in vitro in the anterior hypothalamus using radioactive T as a substrate (Farabollini et al., 1978). In the model (Table 1(c)), two groups of immobility and induction only were matched so that the delay from induction to decapitation was the same in the two groups—animals were sacrificed 15 minutes following a single episode.

The main effect was a pronounced overall decrease of T metabolites, including dihydrotestosterone (DHT) and A, in the immobility group as well as in the induction group, but with a slighter effect. In fact, immobility potentiated the effect of induction, at least in the case of A. E formed in vitro from T (aromatization) was also strongly decreased in both induction and immobility groups.

The overall depression of T metabolism in the anterior hypothalamus found both following induction and hypnosis did not discriminate between the two components. In this respect, the metabolism at a central level differs from the metabolism in the peripheral tissue, as in adrenals. Hypnosis, unlike its effects on glucocorticoids, has no buffer action with respect to T central metabolism, if anything contributing to potentiate the effect of induction.

In order to evaluate if the reduced conversion of T to E and neutral metabolites in the hypothalamus was mediated by alterations in androgen binding, the T binding capacity was analysed in the amygdala (Lupo et al., 1994). The mechanism of androgens action for the control of sexual behaviour (but also of other sexually differentiated behaviours, such as agonistic behaviour), implies the binding to a specific protein in various brain areas (e.g. hypothalamus, preoptic area, and amygdala).

The model applied in this case was the longitudinal protocol (Table 1(b)), with three groups of immobility (0, 15, 30) and three groups of induction (00, 0, 15), matched as previously described.

A specific effect of immobility on T binding capacity, consisting in a decrease at 15 and 30 minutes after the end of the episode, with no effect of induction was found.

On the whole, hypnosis affects the T metabolism in the brain, with a general inhibition of the metabolic enzymatic systems and mechanisms in the same direction of induction. The reduced activity of aromatizing enzymes is of particular interest since the action of T on behaviour is mediated through its transformation into estradiol (McEwen & Krey, 1984).

The depression of T metabolism in the anterior hypothalamus following hypnosis could reflect the depression of sexual behaviour described in stressful situations. Sexual behaviour is in fact under the control of the anterior hypothalamus, with DHT and E acting synergistically to stimulate it in male rabbits (Beyer et al., 1975).
HABITUATION AND HYPNOSIS

The phenomenon of habituation (i.e. reduction of immobility duration following repeated episodes) is one of the constant characteristics of animal hypnosis; it is present in all species sensitive to the treatment and shows a similar pattern in different species (Lefebvre & Sabourin, 1977). Habituation is therefore a strong, reliable model to study the relative effects of induction and hypnosis, and to analyse the variable ‘susceptibility’.

The protocol developed to obtain habituation (Table 1(d)) was a long-term treatment, as follows: repeated episodes of hypnosis in consecutive days (five trials per day) until habituation was reached. The criterion of habituation was when duration of immobility remained below 45 seconds in all the trials of two consecutive days; this was associated with the persistence of reduction in the next six days of treatment with induction.

Plasma corticosterone and ACTH were measured along the treatment at various intervals of the habituation protocol: weekly (on days 1, 8, 14), at habituation, and on the final day of treatment (Farabollini et al., 1981). In order to follow the temporal development of habituation, basal levels were measured (i.e. in blood samples taken just before the first daily trial).

All animals reached the criterion of habituation in different periods of time (mostly between days 8 and 14). Immobility duration was significantly reduced starting from day 6.

Our findings proved the process of habituation as being associated with the activation of the adrenocortical system. Plasma levels of C increased gradually during the treatment, with a peak at habituation and no significant recovery afterwards, when higher levels were maintained during the period of induction only.

A positive correlation between C concentrations and duration of habituation was found: the longer the time needed to reach habituation, the higher the levels of C. This was interpreted as a specific effect of the repeated exposure to the treatment (IND + HYP).

ACTH showed a tendency to increase at habituation, with a significant recovery afterwards. The increase of C plasma levels seemed to be specific to the development of habituation. During the treatment, the duration of hypnosis gradually diminished until it was almost abolished. As a consequence, in the block (IND + HYP) there was a gradual prevalence of IND, which was the only treatment left after habituation was reached. In this situation, effects of induction could be less and less compensated by hypnosis; this could explain the gradual increase of plasma C during the habituation process and its subsequent maintenance by the manipulative procedure of induction. In this process, ACTH likely works as a starter, activating adrenal cortex with a rapid recovery.

Habituation proved to be reversible following appropriate environmental modifications. In habituated animals, pain induced by formalin injection in the paw re-established susceptibility to hypnosis; this was coupled with typical EEG synchronization, if duration was long enough. The same effect was obtained through morphine injection (Carli et al., 1981). Pain (and morphine) effect on hypnosis duration in habituated animals were antagonized by the opioid antagonist naloxone. Incidentally, these results were further evidence of the activation of an endogenous analgesic morphine-like mechanism during hypnosis, as proved in another set of experiments.

When, after repeated treatment, animals reached habituation, they became unsusceptible (induced unsusceptibility). Since habituated subjects had high levels of C, persistent in the days following habituation, lack of susceptibility in these animals seemed to be a different
phenomenon from what is observed in animals naturally unsusceptible, unsusceptibility being associated to low levels of C.

In conclusion, the adrenocortical system is involved in susceptibility to immobility by restriction and inversion, in its various aspects, as spontaneous susceptibility and unsusceptibility induced through habituation. Re-establishment of hypnosis in habituated animals by alterations of the environment indicates that susceptibility may be manipulated with various procedures, in both directions.

Circulating sex hormones (T and E), were not affected by the process of habituation. However, when T metabolism and the conversion of T to E (aromatization) were measured in the anterior hypothalamus in vitro (incubation of the tissue with radioactive T as substrate), habituated animals were different from controls, with an overall increase of T metabolites in habituated animals, significant for DHT and E (Farabollini et al., 1981).

This long-term effect associated to habituation is different from the acute, short-term decrease of T metabolites in the hypothalamus 15 minutes after a single episode of immobility (Farabollini et al., 1978). On the whole, neuroendocrine modifications in habituated animals points to a re-arrangement of the stress-response system to a new ‘steady state’, with high levels of circulating corticosterone and increased sexual hormones metabolism in the anterior hypothalamus. This steady condition of different reactivity can be reversed, however, with appropriate stimuli, such as pain (Carli et al., 1981).

GENERAL CONCLUSIONS
This is a report of experiments on the neuroendocrine aspects of animal hypnosis in rabbits, proving the involvement of the pituitary–adrenocortical system and pituitary–gonadal system and allowing us to draw some conclusions on the function of animal hypnosis.

Peripheral modifications of corticosterone and testosterone plasma levels following induction were typical of the stress-response, with a marked and long-lasting (at least until 15 minutes after the end of the episode) increase in C, and a parallel reduction of T. Similar findings were obtained with physical restraint, one of the most common stressors, confirming the nature of induction as an aversive stressful event (Porro & Carli, 1988).

When induction was followed by immobility, there was a recovery of both hormones to control levels within 15 minutes; on the contrary, there was no recovery during the empty time (matched with hypnosis duration) following the induction.

The hypothesis is that hypnosis functions as a sort of buffer system, re-establishing the endocrine balance with respect to the effects of the stressful event, represented by the manipulative procedure of induction. This interpretation is supported by the electrophysiological pattern of response during hypnosis, with EEG synchronization.

The compensatory effect of hypnosis is likely to work at the peripheral level; a dissociation between induction and immobility, with hypnosis re-establishing the pre-induction balance, was present also in the adrenals, where the metabolites of both the biosynthesis path of corticosteroids and of adrenal androgens were modified accordingly to plasma alterations.

The finding of a depression of T metabolites in the anterior hypothalamus following hypnosis, in the same direction of induction, suggested that the recovery function of hypnosis is limited to the stress-response system.
The hypothalamus, perhaps the most interesting part of the brain to behavioural endocrinologists, is the site where hormones activate mating behaviour in adult male vertebrates. In this area, the action of testosterone on sexual behaviour was found to be mediated through its transformation into estradiol by the enzyme aromatase (McEwen & Krey, 1984). It was also proved that the neural circuits controlling behaviour were different from those involved in the hypothalamus–pituitary–gonadal axis, through gonadotropin-releasing hormone, and the cascade of luteinizing hormone and follicle-stimulating hormone, stimulating peripheral secretion of T (Heimer & Larsson, 1967). Therefore, T plasma levels do not necessarily reflect T brain metabolism and aromatization.

The depression of T metabolism could reflect a depression of sexual behaviour described in stressful situations. This raises the question of the possible relation between hypnosis and mating. In other experiments carried out in our lab on amphibia, susceptibility to hypnosis by inversion was related to sex and the condition of mating, with parallel modifications of sex hormones (Lupo et al., 1987).

Susceptibility to hypnosis could be modified, and almost eliminated, through a prolonged repetition of episodes leading to habituation. In habituated animals there was a rearrangement of the stress-response system to a new ‘steady state’ with higher circulating corticosterone; this condition can be reversed by appropriate stimuli, such as pain (Carli et al., 1981).

Looking back, after so many years, to these experiments on animal hypnosis, I realize how interesting the subject was and how many questions remained unanswered. Our group then scattered towards different research fields; however, most of us are still linked by personal friendship and affection. As for Giancarlo Carli, he has played an important role in my scientific career, and it was most fortunate that we could rely one on the other all through our lives.

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A COGNITIVE APPROACH TO PHYSICAL EXERCISE AND SPORT

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ABSTRACT
This paper summarizes some of the results obtained by our group at the Institute of Physiology in Siena where, in the 1970s, Giancarlo Carli founded the School of Sports Medicine. Carli inculcated a deep interest in the relation between cognition and physical activity in students and colleagues. The main focus of our work were the cognitive factors able to influence sport performance, their neurophysiological correlates, the effects of physical and mental training on performance, and the relation between nutrition and physical/cognitive activity. We have shown that: (a) training reduces reaction times, errors, and variability in the performance of attentional tasks; (b) the characteristics of the motor action and of the related motor cortex potential is modified by both physical and mental imagery training; (c) dietary supplementation with omega-3 fatty acids and policosanols improves reactivity and attention, modifies the profile of mood states, and induces changes in the cerebral activity associated with motor action, similar to those observed after physical training; and (d) the glycaemic index of foods is associated with specific levels of cognitive performance relevant to physical activity. We are grateful to Professor Carli to have oriented our interests, encouraged our research, and helped us with his enthusiasm and criticism.

Key words: attention, reaction time, movement-related brain macropotentials, mental imagery, omega-3

Giancarlo Carli has always been interested in sports and, in his teens, he had planned to become a coach. In fact, he became a Professor of Physiology and, in the late 1970s, founded the Graduate School in Sports Medicine at the Institute of Physiology of the University of Siena and created a line of research that, over the years, has produced interesting results and educated several talented professionals in sports medicine. His group research focused on the activity of hormonal changes occurring during exercise and on the functional evaluation of athletes. In this context, his friendship and collaboration with the founder of Also Enervit, Paolo Sorbini, was very important. Indeed, they shared a curiosity and enthusiasm for sports and physical exercise, and in the development of appropriate nutritional strategies for athletes. Their aim was discouraging the use of doping in sport, studying athletes’ performance during competition, and giving laboratory support to field tests.

During the 1970s, Giuliano Fontani was engaged with Carli in the study of the neurophysiological correlates of attention and emotion in freely moving animals in an open field model. Thus, when Fontani moved into sports research, he started with studies on the
neurophysiological effects induced by physical activity and training. Professor Carli encouraged him to transfer his laboratory experience concerning attention and emotion in animal models to sport applied physiology, as these aspects might be relevant in improving athletes’ performance.

THE INFLUENCE OF PHYSICAL AND MENTAL TRAINING ON MOTOR ACTION REACTIVITY AND NEUROPHYSIOLOGICAL CORRELATES

At that time, standardized protocols for physical training had already been adopted by top level athletes (Fontani et al., 2006). In contrast, the cognitive-emotional factors possibly affecting performance had not been systematically addressed, although many strategies aimed at improving skilled movements, not only by means of the practice of motor execution (Yan & Dick, 2006) but also by mental representations of the motor task (Solodkin et al., 2004) were being developed.

Our aim was to study the physiological variables relating to the psychological aspects of performance and their changes after mental training (Fontani et al., 1999; Fontani & Lodi, 2002). Specific indices of brain activity, such as event-related potentials (ERP) are associated with motor preparation and execution, and some electrical brain potentials are closely related to movement (Kornhuber & Deecke, 1965; Shibasaki et al., 1980) and to skilled motor activities (Papakostopoulos, 1978; Fattapposta et al. 1996; Fontani et al., 2001). Learning modifies these profiles.

A sequence of brain potentials, movement-related brain macropotentials (MRBMs), occurs in relation to the execution of skilled movements (see Figure 1) (Chiarenza, 1991; Fattapposta, et al., 1996). MRBMs have been observed during the performance of skilled tasks in both normal developmental and pathological conditions (Chiarenza et al., 1983; Chiarenza, 1986) and have been studied in trained and untrained subjects, where differences have been described as a consequence of long-term practice (Fattapposta et al., 1996; Di Russo et al., 2005).

Specific components of MRBMs occur during pre-motor, motor, and post-motor periods. In particular, a negative phase potential called Bereitschaftspotential (BP, readiness potential) has been recorded in the pre-motor period (Kornhuber & Deecke, 1965). This potential reflects various motor and non-motor neural processes linked to motor preparation (Brunia, 1988; van Boxtel & Brunia, 1994); it has been widely studied, but the results are controversial. In some cases, a reduction of Bereitschaftspotential amplitude was described in association with the uninterrupted repetition of motor activities (Kristeva, 1977) and with improved performance (Fattapposta et al., 1996). In other studies, the BP amplitude was found to increase after acquisition of a skilled motor task (Taylor, 1978), by paying attention to the movement (Grunewald & Grunewald-Zuberbier, 1983), by the high level of preparation required for complex sequences of voluntary movements (Papakostopoulos, 1978; Kristeva, 1984). In the motor period, a pre-motion positive wave followed by a number of waves related to the onset and execution of the movement has been described (Deecke et al., 1969) (see Figure 1).

In particular, the motor cortex potential (MCP), a negative potential occurring in the earliest part of the motor period, has been considered an index of response-generated afferent activity from muscles (Papakostopoulos et al., 1975) and is affected by practice (Fattapposta, et al., 1996). Less is known about the other waves recorded during the motor period. N1 has been described as a motor component and P2, recorded during the motor completion period,
as a somatosensory component (Chiarenza, 1991), while skilled performance positivity (SPP), a positive wave occurring in the post-motor period, seems to increase with the accuracy of the performance (Papakostopoulos, 1978). Despite some doubts in the interpretation of these potentials (Chiarenza, 1991), they can be considered interesting markers of movement, particularly of skilled motor actions, and can be used to monitor the cerebral effects induced by training.

One of our earliest studies was aimed at evaluating the MRBM waveform modifications possibly occurring in correspondence with a finger movement produced to press sequences of keys during attentional tasks. Three groups of subjects were enrolled in the study. One of them performed a simple reaction time test (Alert test, A), in which the subjects had to press three keys of a keyboard in a precise sequence when a figure appeared on the computer monitor. The second group performed a Choice test (CH), a complex reaction time test, in which the participants had to press the three keys in a different order when one of two different figures appeared randomly on the screen. The third group of subjects performed the Choice test with the addition of a Go/No-Go paradigm (CHNG) in which participants had also to repress an unsuitable response. All subjects were tested before and after 10 days of training on the three tests. Electroencephalography (EEG) and electromyography (EMG) were recorded during the tasks.

The results of this experiment led to the conclusion that a short lasting period of training of a motor action had not only effects on the execution of movement, but also on the associated MRBM profiles. The effects were more pronounced on the Choice and Choice + No-Go tests.

The profiles of MRBMs recorded during the Alert test differed from those observed during CH and CHNG tests, as peak latencies and wave durations occurred earlier in A. Differences between CH and CHNG, which require complex central signal processing and high mental ef-
After training, reaction times (RTs) and their variability were reduced in both the CH and CHNG tests, while no training effect was observed in test A. The main change in MRBMs was observed in the motor period. It concerned the MCP duration which was reduced in A, CH, and CHNG (see Figure 2). The pre-motor period showed a significant reduction of pre-motor potential (PMP) duration only in the CHNG test. Moreover, the correlations between the MRBMs recorded in the three tests (A, CH, and CHNG) and reactivity (measured by EMG latency and RTs) showed that the PMP duration was the best predictor of the latency and duration of the brainwaves related to the same motor action. This suggested that MRBM waves are strictly related to the motor action.

The results confirmed that the effects of training were more pronounced in the tests involving complex central processing (Fontani et al., 2007). The main effects of training on MRBMs concerned the waves recorded after the presentation of the imperative stimulus (the last stimulus requiring the response), and consisted of a reduction of the latency of the peaks occurring during the pre-motor, motor, and post-motor period. The amplitude of BP, a wave recorded before the imperative stimulus, increased after training, which is in line with earlier studies describing an increase of BP amplitude after acquisition of a skilled motor task (Taylor, 1978).

**Figure 2.** Effect of training on MCP duration. Alert test (A), Choice (CH), and Choice + No-Go (CHNG) tests.
and can be due to enhanced attention (Grunewald & Grunewald-Zuberbier, 1983) or to the high level of motor preparation required by the task (Papakostopoulos, 1978; Kristeva, 1984). The PMP duration seems to be crucial for the duration and latency of the successive waves. This pre-motion positivity occurring after the imperative stimulus probably reflects stimulus processing and the development of motor strategies able to react to the presented stimuli (Deecke et al., 1969; Fontani et al., 2007). Thus, it could be suggested that training reduces the time of central processing via a direct action on the central nervous system (Fontani, Migliorini et al., 2009). This is supported by the reduction of the PMP duration in the CHNG test and may indicate that the effects of training are more pronounced on more complex tasks. Altogether, the results show that training reduces the time of motor cortical elaboration of the stimulus and quickens the transfer of motor action to muscles.

MENTAL IMAGERY AND DEVELOPMENT OF SKILLED MOTOR ACTIONS

The above reported results indicate that MRBMs can be used as indicators of motor learning induced by training. MRBMs can be modified also by the mental representation of skilled motor acts (Solodkin et al., 2004) and a number of studies have shown that mental imagery of a motor action improves the motor skill acquisition (Corbin, 1972; Feltz & Landers, 1983; Roure et al., 1998; Brouziyne & Molinaro, 2005; Driediger et al., 2006). The effects of mental imagery training are similar to those obtained by physical training, both of which could be explained in terms of variation of motor cortex neurons activity (Pascual-Leone et al., 1995). Mental imagery affects not only the motor act, but also muscle strength and trophism, thereby raising prospects for the use of mental imagery in the field of rehabilitation (Jackson et al., 2001). The imagery-induced increase in muscle strength is associated with variations of brain activity (Naito & Matsumura, 1994; Ranganathan et al., 2004) which, in turn, is dependent on psychological factors (Masaki et al., 1998; Ranganathan et al., 2004).

In order to assess the relationship between muscle performance, cerebral variables, and psychological factors, and to evaluate the possible role of mental imagery in sport, we designed an experiment aimed at comparing the effects of three different conditions (no training, active training, and imagined training) on learning a skilled motor ability such as a karate action. In particular, we analysed the influences of motor execution and motor imagery training on brain and muscle activity according to the hypothesis that motor imagery could affect these physiological functions (Fontani, Migliorini et al., 2009).

We studied three groups of athletes who had to learn a new motor action (Ura-Shuto-Uchi): Untrained (subjects not performing any training, UT), Action Trained (subjects performing Ura-Shuto-Uchi training daily for 16 minutes, AT), and Mental Imagery (subjects performing mental imagery training of Ura-Shuto-Uchi daily for 16 minutes, MI). The subjects were tested five times, once every seven days. During each test, they performed a series of 60 motor action trials. In Tests 1, 3 and 5, they also performed a series of 60 mental imagery trials. During the trials, EEG, EMG, muscle strength, and power were recorded.
Figure 3: MRBM in the Untrained (UT), Action (AT), and Mental Imagery trained (MI) groups.
Figure 4: Mental Imagery group. MRBM recorded at Cz during Tests 1, 3, and 5
Figure 3 shows a MRBMs profile in expert subjects (A) and the profiles of untrained (UT), action trained (AT) and mental imagery trained (MI) subjects, recorded during Test 5. The UT subjects did not show significant difference over time. In the AT group, training reduced the EMG activation and reaction times calculated at the time of completion of the action. Moreover, muscle strength and power increased significantly. The MI group showed similar effects on muscle strength and power, but did not exhibit changes in reaction times. In this group, the study of MRBMs indicated a progressive modification of the profile of the waves from Test 1 to Test 5 during imagery, with significant variations of the amplitude of the waves related to the pre-motor and motor execution periods. In line with other authors’ findings (Ranganathan et al., 2004), we concluded that mental imagery of a motor action modulates the activity of the neural and muscular structures involved in the motor action. Moreover, our results showed that the effects obtained by the AT and MI groups on muscle strength and power were similar. Analysis of the cerebral activity showed that there was a clear modification of the profile of the waves from Test 1 to Test 5 in the MI group, with significant variations of the amplitude of some peaks (see Figure 4). In particular, mental training increased the negativity of the BP, MCP, and N1 amplitudes. The increase in the negativity of BP, a wave occurring before the imperative stimulus, was correlated with the amplitude of PMP and N1, waves occurring after the stimulus in the first motor period, the motor sensory period. The increase of the N1–P2 interval amplitude was particularly evident at Test 5 with respect to Test 1 at Cz and Fz, correspondent to brain areas where the motor processing waves are best represented. The MCP increase was also in line with other reports indicating higher MCP amplitudes in self-paced skilled movements and no change in subjects with learning disabilities (Chiarenza et al., 1983; Fontani et al., 2007). Nevertheless, a few differences in the effects of motor and mental training on the cerebral correlated motor action were present. They can be summarized as less pronounced increase of the amplitude of the waves occurring during the pre-motor period and the motor period, in particular MCP and N1–P2 in the MI group.

In conclusion, mental imagery can be a useful method to learn and to train skilled motor actions. It can be used to build and consolidate motor sequences and to improve muscular capacities, and can be a valid strategy in sport disciplines, particularly those based on specific skilled technical actions (Fontani et al., 2007). In addition, the changes induced in the brain potentials profiles during training allow us to evaluate the effects of motor imagery and monitor the progressive development of a skilled motor action.

COGNITIVE EFFECTS OF DIETARY SUPPLEMENTATION: OMEGA-3 AND POLICOSANOLS

In the perspective of the relation between nutrition and physical activity, another research line that we developed across the years concerns the effects of food supplements on cognitive functions. In particular, we have shown that, in healthy subjects, dietary supplementation with omega-3 fatty acids and policosanols improves reactivity and attention as well as mood states and emotional control (Fontani, Lodi et al., 2009), while we failed to detect omega-3 induced effects on motor-related brain potentials. Our results on attention and reactivity are in line with the current literature showing that omega-3 fatty acids may play a role in cognitive development (Jho et al., 2004), increase learning ability (Neuringer et al., 1994; Sears, 2002), and improve cognitive performance (Willatts, 2002). The omega-3 efficacy on cognitive performance is associated with many beneficial effects: they are considered an important
anti-inflammatory factor (Yehuda et al., 2002), show inhibitory effects on tumorigenesis, and reduce mortality from cardiovascular diseases (Fletcher & Ziboh, 1990; Piomelli 1994; Yehuda et al., 2002; Fontani, Corradeschi, Felici, Alfatti, Bugarini et al., 2005; Corradeschi et al., 2006). Omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are manufactured in the body using alpha-linolenic acid as a starting point (Arita et al., 2003). In the nervous system, polyunsaturated fatty acids are released from membrane phospholipids when neurones are stimulated by neurotransmitters and are locally metabolized, giving rise to a series of active products, such as the eicosanoids, which may act in the intracellular environment as neuronal second messengers and influence neuromodulation, synaptogenesis (Haag, 2003), synaptic plasticity (Martin & Bazan, 1992), and signal transduction (Jones et al., 1997). In particular, they are involved in cholinergic, serotoninergic, and catecholaminergic synaptic transmission (Piomelli et al., 1991; Horrobin et al., 2002; Haag, 2003).

In other experiments (Fontani et al., 2000), we observed that policosanols, a mixture of higher aliphatic primary alcohols derived from wheatgerm oil and sugarcane wax which can lower blood cholesterol levels (Larsson et al., 2004), can reduce reaction time in attention tests and affect some event-related brain potentials, increasing their amplitude and reducing the latency of some peaks, as previously observed (López & Ortega, 2003). From these experiments, we can infer that event-related potentials are influenced by omega-3 and policosanol.

Since policosanol and omega-3 have similar effects on reaction time and related brain activity, we hypothesized that the association between policosanols (P) and omega-3 (O-3) could affect reactivity in simple and/or sustained attention tests and modify the profiles of MRBM. Thus, we carried out a study including conditions requiring prolonged high levels of mental engagement. In this study, complex reactions in subjects (karateka) trained to react quickly and with precise motor sequences to sudden stimuli have shown that after 21 days of dietary supplementation (Test 2 vs. Test 1 performed before O-3 and P supplementation), the subjects reduced their reaction times and increased the vigour sensation while decreasing the scores of anger, anxiety, fatigue, confusion, and depression measured by the POMS (Profile of Mood States) test.

Figure 5: Latency of PMP (Pre-Motor Potential: Pk1, first peak and Pk2, second peak) and EMG recorded before and after omega-3 supplementation and during control period
Analysis of the event-related brain potentials showed a reduced latency of MRBMs. In particular, the potentials recorded in the pre-motor period and motor period occurred earlier and the latency of EMG activation was reduced (see Figure 5). After a further 21 days from the last O-3 + P supplementation (Test 3), the positive effects on the mood state persisted, while the reaction time, EMG, and brain potential latencies increased, although their values remained at lower levels than in the first test. The placebo group did not show any significant differences in Tests 2 and 3 with respect to Test 1 for either POMS or reactivity and brain potentials. These results confirm our previous experiments (Fontani, Lodi et al., 2009) in which omega-3 and policosanols affected reactivity and neurophysiological measures and are in line with similar experimental approaches (Stoll et al., 1999; Lòpez & Ortega, 2003; Savva et al., 2004; Fontani, Corradeschi, Felici, Alfatti, Migliorini et al., 2005). Policosanols reduce reaction time in simple go/no-go and choice attention tests and reduce the latency of the event-related potentials after the stimulus (Lòpez & Ortega, 2003). Omega-3 polyunsaturated fatty acids improve mood profile and reduce reaction time in complex attention tests, particularly those involving the go/no-go paradigm, while the effects on the event-related potentials are limited to an increase of amplitude of the waves occurring before and after the stimulus during the go/no-go test (Savva et al., 2004; Fontani, Lodi et al., 2009).

The omega-3 induced variation of cerebral waves related to movement strengthens the hypothesis of a direct action of omega-3 fatty acids and policosanol on the central nervous system (Fontani, Lodi et al., 2009). The mechanisms involved may be related to omega-3 acting as a controller of neuronal excitability (Puri et al., 2004) and modulating many of the signal transduction mechanisms operating at the synaptic level (Haag, 2003), while policosanol can facilitate membrane conductivity (Lòpez & Ortega, 2003; Peet & Stokes, 2005), matching some of the effects of omega-3 and being particularly effective on reactivity (Lòpez & Ortega, 2003).

GLYCAEMIC INDEX AND ATTENTIONAL CAPACITY

Another important parameter related to the capacity to maintain and improve attention during physical activities characterized by a high commitment of attention is the blood glucose level. This variable should be kept constant, as glucose is the main energy source for the brain and adequate blood levels of carbohydrate are necessary for the maintenance of optimal cognitive function (Ciok & Dolna., 2006; Nilsson et al., 2009). The speed with which it is transported from food to blood is a function of the glycaemic index (Scholey et al., 2001; Benton et al., 2003).

The concept of the glycaemic index (GI) was introduced in 1981 by Jenkins and colleagues (1981) and is widely recognized as a reliable method to predict the rise of blood glucose caused by various foods and, consequently, the associated rising of blood insulin (McLaren, 2000; Foster-Powell et al., 2002; O’Reilly et al., 2010).

Many studies have shown that, compared to placebo, an increase in glucose is associated with better cognitive performance, both in humans and animals (Kaplan et al., 2000; Park, 2001; Benton et al., 2003; Flint & Turek, 2003; Lieberman, 2003; Ingwersen et al., 2007; Gilsenan et al., 2009; Nilsson et al., 2009). Although the evidence is not always consistent, there is evidence that carbohydrate ingestion may improve concentration, reaction times, learning ability, mood, memory, and psychomotor performance; likewise, an insufficient glu-
Glucose supply causes a worsening of these skills/tasks (Ciok & Dolna, 2006; Scholey et al., 2001; Papanikolaou et al., 2006; Hoyland et al., 2008). Glucose uptake by the brain depends on brain activity and, thus, is also a function of cognitive demand, as shown by the increased glucose metabolism in the brain areas involved in cognitive activities (Hoyland et al., 2008). Several studies have shown that low GI foods, causing a smaller increase in postprandial release of insulin, lead to a lower uptake of glucose by insulin-sensitive tissues such as the muscles, liver, and white adipose tissues that facilitate the flow of glucose from the blood to the brain, allowing the attainment of improved cognitive performance compared to high GI foods (Kaplan et al., 2000; Benton et al., 2003; Ciok & Dolna, 2006; Ingwersen et al., 2007; Gilsenan et al., 2009; Nilsson et al., 2009). This could be particularly important during activities requiring constant high levels of attention, whose decrement is the main symptom of mental fatigue.

In a preliminary experiment we studied the variation of attention and related physiological parameters in healthy subjects after intake of carbohydrates of different GI in healthy volunteers. The experimental sessions were held on Day 1, 20, and 40 in which each subject randomly received a solution containing sucrose (high GI), fructose (low GI), and a sweetener (placebo). Blood collections were held at 30, 60, 90, 120, and 150 minutes after solution intake. An attention barrage test, concomitant with EEG recording, was performed at 30, 90, and 150 minutes. The results showed that the average blood glucose levels had different profiles: after sucrose there was an increase of blood glucose, with a peak at 30 minutes, followed by a rapid decrease. Fructose showed a lower increase after 30 minutes and a slow decrease in the...
following minutes, while placebo intake was followed by a slight decrease of blood glucose (see Figure 6). The analysis of the barrage test did not show differences between sucrose and fructose after 30 minutes, but in the following tests, the number of errors was lower in the fructose test. EEG frequency analysis showed an increase of high frequencies after fructose during barrage in the second and third test (Migliorini et al., 2009). These data confirm that the glycaemic index of carbohydrates modulates cognitive performance and that attentional capacity is reduced when blood glucose levels are low. Indeed, the rapid reduction in blood levels of glucose occurring after the initial peak (30 minutes) was accompanied by an equally marked decrease in attentional capacity. Moreover, in agreement with data from other studies (Thomas et al. 1991; Scholey et al. 2001; Ingwersen et al. 2007; Simpson et al. 2007; Nilsson et al. 2009), the results of our experiment showed that the intake of low GI carbohydrates, such as fructose, can counteract the decline in attentional performance and, thus, prevent the effects of mental fatigue. The results of our experiment are further supported by the analysis of EEG frequencies, which showed a marked increase in high frequencies (in particular $\gamma$) during performance of attentional tests after fructose intake. This is in agreement with data that showed a strong link between $\gamma$ EEG frequencies and processes of selective attention: higher levels of the latter are related to an increase of $\gamma$ waves during EEG recordings (Aoki et al., 1999; Ray et al., 2008). Minor decreases in blood sugar following consumption of low GI carbohydrates, therefore, seem to correspond to high levels of high frequencies and lower levels of low frequencies recorded during performance of attentional tests.

These findings suggest that proper protocols of carbohydrate intake before and during exercise can prevent significant reductions in attentional capacity during competition, which is particularly useful in open skill sports in which high levels of sustained attention are required (Migliorini et al., 2009).

CONCLUSION

Our findings confirm the relevance of cognitive competences and training in physical exercise and sports, and indicate that the original intuition of Giancarlo Carli – the importance of laboratory experiments to support research in many open skill sport disciplines – was valid and is still fruitful.

Our studies on the cognitive factors involved in the improvement of sport performance and on their modulation by psychological and nutritional variables moved from the multifaceted cultural atmosphere we experienced at the Institute of Human Physiology in the 1970s, when the newly founded School of Sport Medicine started its activities. They are a product of our education as neurophysiologists received in Carli’s lab and of the interest in cognition that had been a marker of the laboratory since Professor Carli obtained a Chair in Siena. In those years, the main characteristic of the lab was an enthusiastic multidisciplinarity which allowed each of us to develop her/his own talents in research on the physiology of exercise and sport. We are grateful to Giancarlo Carli because he oriented our interests, encouraged our research, and helped us with his criticism and advice. Finally, we have to say that, beyond research, it has also been a pleasure to have had the opportunity to rigorously educate so many medical doctors in sports medicine in the friendly, collaborative, and relaxing context created by Giancarlo Carli.
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THE INSTITUTE OF HUMAN PHYSIOLOGY IN SIENA: A MIX OF FANTASY AND SKILLS

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ABSTRACT

On 13 March 1982 it was snowing in Siena, a quite exceptional event. On that day, I started my experience as a medical student in the lab of Professor Giancarlo Carli. Siena University's Institute of Human Physiology was located in a wonderful place close to Siena's old walls, the Laterino. I was there between 1982 and 1996, years that I shared with many colleagues whom I would like to recall here. Indeed, although personal talents are important, the interactions with colleagues and the opportunities and difficulties occurring in a researcher's life can be even more important. In this paper, I present a number of elements that contributed to my scientific career together, against, in parallel, in discussion, and in silence with Giancarlo Carli.

Key words: Siena's physiology, CNS, hypnosis, hormones

THE BEGINNING

Professor Giancarlo Carli was used to fixing the date for the medical students’ examinations in human physiology on the last day of the carnival season. This was also the case in 1982. The lectures had been difficult and few students were ready to take the exam. However, the exam went well for all of us, the atmosphere was relaxed, and a nice discussion ensued afterwards. The subject was the study of human physiology and the professor's aim was to sound out the students' interest in doing research in this field. I do not know why I declared my interest in it. Indeed, I had no research experience and, in the few months that I had spent at the university, I thought that becoming a surgeon would have been great. Thus, I was asked to participate in the experiment planned for the next day and, in spite of the snow, I was in front of the Institute's door at 9 a.m. on 13 March. Everything was ready for the experiment, but the physiologists that were to perform it could not reach Siena owing to the snow and the experiment was postponed. Yet, that day gave origin to a new life for me and to my encounters with my many colleagues at the Institute of Human Physiology.

THE 'JOINT LAB' AND OTHERS

The experiment to be carried out concerned the characterization of articular nerve afferents in the cat hip joint, which was a difficult task. I remember the time spent, initially with Angelo Taviani, Giovanni Biasi, Alessandro Rossi, Maurizio Bisogni, and then alone, testing the many tools necessary to record action potentials from cortical neurons (Aloisi et al., 1988). That experimental setting required a mix of skills—from microsurgery and neurophysiology
to electronics—and was a good test to select researchers in physiology. We were asked to manually produce most of the tools used during the experiments and I was happy when, using incredibly unknown things, I was able to build a tungsten microelectrode with a glass coating to record neural activity.

The years spent in that lab gave me the opportunity to be slowly introduced to the world of central nervous system activity and to meet colleagues like Mountcastle and Moruzzi, Berlucchi and Rizzolatti. It was a great human and scientific experience.

Near the neurophysiology lab, there was a lab with a box placed in the middle of the room and containing a cage. In that cage, rabbits were tested for animal hypnosis (tonic immobility, TI). Giancarlo taught me how to hypnotize rabbits. It was really fun to be able to block these animals in an unnatural position. I do not know if other researchers in the world are still doing these kinds of experiments. However, they were immensely impressive.

Many abilities were required at the same time in that lab. Giancarlo’s aim was to study the mechanisms that completely suppress painful information during tonic immobility and to assess the endocrinological correlates of both TI and TI-related pain modulation. The possibility of inducing TI in animals is still an interesting topic as not all has been clarified concerning the reasons why TI suppresses any sign of pain in rabbits subjected to formalin-induced inflammation.

Independently of the scientific advancements in TI, these experiments deeply influenced our group, including at that time Fulvio Grazzi. In fact, our interest slowly focused on pain and we started to consider pain our main topic (Aloisi, Lupo et al., 1993; Aloisi & Carli, 1996; Aloisi, 1997; Aloisi et al., 1997). A few years earlier, Giancarlo had been involved in the establishment of the national chapter of the IASP (International Association for the Study of Pain) together with colleagues like Paolo Procacci and later Mario Tiengo, who became my very good friends.

At that time, senior colleagues of Giancarlo were Concetta Lupo, Antonio Viti, Francesca Farabollini, and Giuliano Fontani (see Figure 1). Each of them had a particular research field, but they were also extraordinarily able to exchange their experience and know-how with each other. I was the youngest member of the group and I happily joined in this collaborative atmosphere, which enabled me to integrate most of their experiences into one area of research. Indeed, my main key words are now: pain, central nervous system, gonadal hormones, and sex differences.

Figure 1. The Human Physiology Institute’s personnel in the period 1982–1996
THE ‘PAIN GROUP’

At the beginning of my scientific career, pain was not my main interest. However, I was fortunate to be included in a team with other colleagues who recognized in Giancarlo a useful guide in the field of pain, among them Valeria Bachiocco and Carlo Porro. They often sat in the green armchairs in Giancarlo’s studio and talked for hours. It was a kind of rito.

Carlo Porro represented an exceptional link with other colleagues involved in pain research—Paola Sacerdote, Mauro Bianchi, Alberto Panerai, Gabriele Biella, and Maria Luisa Sotgiu—and we had the opportunity to meet them quite often at several congresses throughout the world. This was a kind of cement that enhanced our desire for collaboration, discussion, and enrichment of the group with different scientific experiences (Aloisi et al., 1992; Aloisi, Porro et al., 1993; Aloisi et al., 1995). I still remember the ‘famous’ night trip through Miami, the ‘dancing crab’ in Bethesda, the escargot in Paris, the dinner with Mario Tiengo and many others in San Diego (see Figures 2 and 3). Each of us was aware of being part of a group in which the will to discuss our scientific interests was the main reason to be together.

Figure 2. The ‘dancing crab’ experience. Left: Paola Sacerdote and Mauro Bianchi; right: Anna Maria Aloisi and Giancarlo Carli

Figure 3. IASP Congress 1993, Paris: Carlo Porro, Anna Maria Aloisi, and Giancarlo Carli; and 3b. Miami 1997: Giancarlo Carli with Carlo Porro and Mauro Bianchi
CHANGES
At the beginning of the 1990s, things changed. I got married, gave birth to twins and started my own research: sex differences in pain. Life became more difficult, but also more interesting owing to many international collaborations that took me far from the influence of Giancarlo.

In those years, the Institute of Human Physiology included a small house with a garden, named 'Il Podere', where Concetta Lupo was measuring steroids with the valuable help of Leda Lodi. Concetta was a pioneer in techniques to measure blood and tissue steroids. I do not remember why she was measuring these hormones in toads, but many other determinations had grown from those experiments. Although I never tried to learn how to perform radioimmunoassay to measure steroids, our collaboration was crucial to my choice of combining the study of gonadal hormones with the study of pain.

In her lab, in addition to measuring steroids, it was always possible to talk. To measure steroids was and still is a quite difficult task, but talking with Concetta was a great pleasure. Her Neapolitan character had not been changed by her many years spent in Siena!

In the same years, Francesca Farabollini led a research group within our Institute dealing with sex differences in the physiology of stress. She was using rabbits, but after her contact with the Brain Research Institute in Amsterdam she introduced the rat model and an ethological approach to the study of sex differences, stress, and also gonadal hormones (Farabollini et al., 1993; Aloisi, Steenbergen et al., 1994). In her lab, I was able to develop a profound interaction with Manuela Albonetti (Aloisi, Albonetti et al., 1993; Aloisi, Albonetti et al., 1994), who was excellent. She taught me to use statistics, to write scientific papers, to love Mexico, and then she disappeared!

The other group active in the Institute at that time was led by Giuliano Fontani, who was involved in the study of the electroencephalogram (EEG) recorded from the cerebral cortex and hippocampus of implanted rabbits. He was really a pioneer in the telemetric recording of the brain’s electrical activity in experimental animals. Recordings were done in the same cage used for hypnosis, but also outside in a very natural environment where the animal’s EEG could be recorded in different phases of its day–night cycle. I still remember the many days spent counting the hippocampal waves printed on thousands and thousands of pages with the aim of determining the frequency or duration of the theta activity (Fontani et al., 1987, 1992).

From Antonio Viti I learned to love jazz and the great truth that to be able to teach something we need to know how to do it!

To complete the picture, I must include the names of others present in those years in the Institute of Human Physiology: the sport physiology colleagues Marco Bonifazi, Gilberto Martelli, and Massimo Capitani, who had a common feature, namely their wonderful, powerful voices; and the technicians Mario Landi, Carmela Masucci, and Claudio Calosi with whom we shared many things.

Two other colleagues who attended the Institute in those years and I wish to mention are Manfred Zimmermann, who collaborated with Giancarlo on many pain projects organized in/ by the Institute, and Enrica Santarcangelo, who introduced, together with Giancarlo, the study of human hypnosis in our Institute.

In 1996, the Institute of Human Physiology was transferred to a new campus. Many things ended.
MULTIDISCIPLINARITY WAS AN ADDED VALUE

From these few memories of our ‘old’ Institute, it becomes clear that human physiologists in Siena were strictly ‘multidisciplinary’. This feature was Giancarlo’s real contribution to Italian physiology, a habit that most of us adopted. This was an excellent approach, as shown by the fact that after 30 years of global research at micro/nano levels in many fields, including pain, the scientific community is developing a renewed interest in behaviour and integrated systems.

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THE UNPREDICTABLE CONSEQUENCES OF A SCIENTIFIC DISAGREEMENT

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ABSTRACT

This paper reviews my scientific collaboration with Professor Giancarlo Carli through three decades. In the 1980s he worked hard to persuade me to study human hypnosis, since at the time I did not regard hypnosis as a suitable subject for physiological studies; at present I am nearly the only physiologist who has aimed her entire scientific activity to investigating the physiological correlates of hypnotizability. In this paper I comment on only two of the implications rising from our experiments. The first concerns the ability of highly hypnotizable individuals (Highs) to embody sensorimotor images in relation to the perception of involuntariness in action; the second refers to the Highs' greater endothelial nitric oxide availability which may induce lower vulnerability to cardiovascular disease, and could also account for modulation of brain functions. Giancarlo Carli has impressed a deep mark on my research and, as a consequence, on my whole life. I feel greatly in debt to him.

Key words: hypnotizability, hypnosis, imagery, motor control, endothelial function, voluntariness

A SCIENTIFIC DISAGREEMENT

I met Professor Carli for the first time after graduating in medicine, when hypnosis and pain were not my scientific interests. At that time, I was attending the School of Medical Psychology in Siena, and in 1983 I went to see him with the simple request to work for my post-graduate thesis in his physiology lab. I was greatly impressed by his kindness and humanity but, when he proposed a thesis project on hypnotic analgesia, I felt deeply disappointed, as in my opinion hypnosis did not belong to the physiology domain. My objections were rooted in my early experience of physiological research in the lab of Professor Pompeiano, in Pisa, where they studied motor control. There I had seen physiologists addressing 'solid' facts, as reflex reactions and voluntary movements surely are. Hypnosis, provided it was a fact, was far from 'solid'. Therefore, the negotiation about my thesis, although fair, was hard and time consuming on both sides. Eventually, we agreed on a compromise: the thesis would concern the effects of hypnosis on spinal cord excitability.

I must confess that I did not expect that the spinal cords of subjects with different hypnotizability might react differentially to electrical stimulation, or that any physiological definition of hypnosis might ever been achieved.

In a rather unsettled psychological state, I began to evoke H-M cycles (Hoffmann, 1922) in the soleus muscle of subjects with high (Highs) and low (Lows) hypnotizability, in and out of hypnosis. H-M cycles include the H reflex, a monosynaptic reflex response to the electrical
stimulation of a nerve proprioceptive afferents, and the M wave, which is elicited by the direct stimulation of motor fibres (see Figure 1).

Figure 1. H-M recruitment curve. (A) Stimulation of a nerve containing motor and proprioceptive fibres induces both orthodromic and antidromic volleys. Motor fibre activation (1) elicits a muscle motor response orthodromically (M) and invasion of the motoneuron pool antidromically. Proprioceptive fibres activate the motoneuron pool orthodromically (2) producing the H reflex and are ineffective at muscle level owing to the structure of the neuro-muscular synapse. (B) Since sensory fibres have larger diameters than motor ones, the H reflex threshold is lower than the M wave’s one. With increasing stimulation intensities, motor fibres are activated and invade the motoneuron pool, which reduces the number of motoneurons able to respond to the orthodromic volley led by the sensory afferents. Thus, with increasing M amplitudes, H amplitude decreases.

The H reflex is a flexible tool for studying motor control (Knikou, 2008; Chen & Zhou 2011). At that time a group of French researchers headed by E. Pierrot-Deseilligny was just developing the double-shock techniques able to reveal the activity of specific spinal interneurons in humans (Pierrot-Deseilligny & Mazelet, 2000). I considered that, while pretending to study the effects of hypnosis on spinal cord excitability, I might work on more interesting things ...
CHANGING MY OPINIONS

In a few months the situation became embarrassing because I seemed unable to reproduce the H-M cycle during simple relaxation sessions in Highs, although I had never failed when working in Pompeiano’s lab in subjects not selected for hypnotizability. This experimental impasse forced me to consider the possibility that being a High may affect experimental conditions. Indeed, in Highs, during long-lasting relaxation, skin conductance decreases and this causes artefacts in the H-M cycle recordings (see Santarcangelo & Sebastiani, 2004).

To make short the long story that started from this observation, I say only that eventually we overcame the problem of skin conductance and demonstrated that high hypnotizability is associated with high habituability of the H reflex, independently of hypnosis (Santarcangelo, et al., 1989).

The enthusiasm of a medical student, Knut Busse, who joined our adventure, and the interest of Ernest Hilgard, who considered our results ‘intriguing’ (Figure 2), encouraged us to go on. In his thesis Knut applied multi-linear regression and time series analysis to randomly evoked H reflexes and showed that, only in Highs, the H reflex amplitude depends on the amplitude of the H reflex occurring three intervals earlier in the stimulation series, which means that the spinal cord learning/memory characteristics of Highs and Lows are different (Busse, 1991).

Figure 2. Letter by Ernest Hilgard to Giancarlo Carli. It refers to the earliest paper published by Carli’s group on the hypnotizability-related modulation of spinal cord excitability in and out of hypnosis (Santarcangelo et al., 1989).

We worked also on the F wave (Eccles, 1955), a motor response evoked in a small part of a motoneuron pool antidromically excited through motor fibres. F wave is due to cells that, for their short post-discharge refractory period, can be activated also by the orthodromic volley of the afferent fibres concomitantly stimulated. The F wave is useful to disentangle the excit-
ability of pre- and post-synaptic motoneurons because its frequency of occurrence, amplitude, and latency depend on the motoneurons’ post-synaptic excitability only.

We found that, during simple relaxation as well as during hypnosis, the post-synaptic excitability of the motoneuron pool of the abductor digiti minimi muscle decreases in the right hand of Highs and does not change in Lows, which is in line with other evidence of hemispheric asymmetries in Highs (Gruzelier, 2006; Naish, 2010).

Another challenging result was obtained after hypnotic induction (Danziger et al., 1998). We found that the suggestions for analgesia administered during nociceptive stimulation are associated with reduction of both the perceived pain intensity and the amplitude of evoked brain potentials. However, the amplitude of nociceptive flexor reflex response (RIII) is decreased in some Highs and increased in others, which was in contrast with the generally reduced RIII amplitude observed by other authors (Kiernan et al., 1995). A possible explanation for the discrepant responses is suggested by recent evidence showing that in the general population the amplitude of RIII is increased by distraction from nociceptive stimulation, although pain perception is reduced (Roy et al., 2011). Thus, it is conceivable that the suggestion of analgesia is worked out by cognitive processes that may differ among individuals (who may focus attention on the instructions for analgesia or divert attention from stimulation) and these differences underlie the variability of motor reactions observed in the High population.

In the same period, anecdotic observations on subjects performing autogenic training or Vipassana founded the view, developed in later works, that relaxation is a true cognitive task (Sebastiani et al., 2005) and that prescribing a relaxation technique to patients may require a preliminary assessment of their cognitive style (see Santarcangelo & Sebastiani, 2004). I also initiated a collaboration with the Institute of Clinical Physiology of the National Council of Research, in Pisa, on the hypnotic modulation of heart rate variability (HRV). The results showed that during neutral hypnosis Highs increase the absolute power of both the parasympathetic (HF) and sympathetic (LF) components of HRV, although the former rises significantly more than the latter (Santarcangelo et al., 1992). This concurs with later observations conducted on the normalized values of the HRV components (HFn, LFn: absolute values divided by the total power spectrum of the RR series obtained from ECG) indicating a parasympathetic prevalence in Highs (De Benedittis et al., 1994). At that time, when the debate on the ‘autonomic space’ was just beginning (Berntson et al., 1994), the concomitant increase in the absolute power of both HF and LF appeared surprising, but it challenged for the first time my scepticism about the existence of the ‘hypnotic state’. Indeed, it pointed out to me, for the first time, that hypnosis was somewhat different from deep relaxation.

Those years (1984–1991) were very exciting. Professor Carli invited Basil Finer, Helen Crawford, and Giuseppe De Benedittis to visit his lab and give lectures, and in the meetings we attended together I had the opportunity to meet many leading figures of the field—Istvan Metzaros, Eva Banyai, and Vilfredo De Pascalis, among others. I learned from each of them and enjoyed the atmosphere of intelligent open-mindedness in the lab.

Unfortunately, for personal reasons I had to give up research for several years. I missed the lab. Finally, owing to the interest of Professor Brunello Ghelarducci in my experience and know-how, I attained a research position at the University of Pisa and very soon Giancarlo and I started a fresh collaboration on new projects. We did not decide to work together again, it just happened.
NEW IDEAS

Due to the priceless collaboration of many colleagues—physiologists, psychologists, cardiologists, neurologists, and mathematicians—my work during the last decade has opened up new prospects into research on the physiological correlates of hypnotizability. We have now provided consistent evidence that the cognitive trait of hypnotizability accounts for part of the physiological variability in many aspects of daily life (Carli, Huber et al., 2008), ranging from posture (Santarcangelo, Scattina, Carli et al., 2008; Santarcangelo, Scattina, Orsini et al., 2008; Santarcangelo et al., 2010) and locomotion (Menzocchi, Paoletti, Carli et al., 2010; Menzocchi, Paoletti, Huber et al., 2010) to imagery (Carli et al., 2006, Carli, Cavallaro, Rendo et al., 2007; Carli, Cavallaro & Santarcangelo, 2007; Santarcangelo et al., 2010), visual recognition of haptically explored objects (Castellani et al., 2011), written language (Marinelli et al., 2011), and cardiovascular activity (Jambrik, Chunzeng et al., 2004; Jambrik, Santarcangelo et al., 2004; Jambrik et al., 2005a, b; Carli, Huber et al., 2008; Santarcangelo, Balocchi et al., 2008; Santarcangelo, Carli et al., 2008).

Some of our results are summarized by Mark Jensen in this volume. I want mention here only two findings which I think are relevant both in the field of the physiological correlates of hypnotizability and in the realm of hypnosis.

The first finding concerns the bodily effects of imagery and could inspire a novel interpretation of the perception of involuntariness in action reported by Highs after imaginative suggestions. In fact, our results indicate that involuntary motor responses can be modified, in Highs, by imagery of the sensory context implied in the reflex (Santarcangelo et al., 2010). It is well-known that, in the general population, the imagery of voluntary movements is associated with excitability changes of the corresponding motoneuronal pools (Jeannerod, 2001; Fourkas et al., 2006; Li, 2007; Léonard & Tremblay, 2007; Bakker et al., 2008; Liepert & Neveling, 2009), but it was hardly expected that imagery could activate the sensorimotor circuitry responsible for involuntary responses. In this light, the ability to behave according to suggestions, up to experiencing involuntariness in action, may depend on an automatic, suggestion-triggered translation of mental images into activity of specific neural circuits. This effect may be described as a sort of ’sensorimotor synaesthesia’ and can occur independently of the modulation of the functional connections between the prefrontal cortex and anterior cingulate.

The second finding concerns the hypnotizability-related differences in the endothelial function (FMD); that is the vasodilating response of arteries to occlusion, largely mediated by the release of nitric oxide (NO) from endothelial cells. We have found that, in response to nociceptive stimulation and cognitive stress, the FMD assessed in the brachial artery is consistently better in Highs than in Lows (Jambrik, Chunzeng et al., 2004; Jambrik, Santarcangelo et al., 2004; Jambrik, Carli et al., 2005; Jambrik, Sebastiani et al., 2005) and the difference does not depend on hemodynamic factors (Paoletti et al., 2010). This result has a clinical implication, for low FMD is predictive of cardiovascular disease (Green et al., 2011) so Highs are likely to be less vulnerable than Lows to this pathology. Clinical trials are in progress to test this hypothesis.

In addition, since it is expected that a better endothelial function reflects larger availability of NO in brain vessels, I wonder whether NO could play a role in shaping the hypnotizable brain. Indeed, there is evidence that after diffusion into the extracellular compartment, NO acts as a neurotransmitter and/or neuromodulator and, in this function, it affects the
release of acetylcholine and dopamine in the striate region of the rat (Guevara-Guzman et al., 1994). Due to its influence on the regional content of brain dopamine (Nabeshima et al., 1987; Loscher et al., 1991), the NO may influence the functional balance between the activity of cortical and subcortical areas accounting for more stable or flexible cognitive functions (Cools & D’Esposito, 2009; Darvas & Palmiter, 2011). Thus one may suggest that greater availability of NO in the brains of Highs does ultimately mould cognitive characteristics and behavioural responses such as the ability to comply with hypnotic suggestions.

CARLI’S DEEP MARK IN MY SCIENTIFIC CAREER
Professor Carli won the battle against my scientific prejudices long ago. Now I am proud to claim that, in spite of my early doubts, I have devoted my scientific career entirely to the search for physiological correlates of hypnotizability. This is a subject that I, and the many students attending my lectures at the University of Pisa, find fascinating.

In all modesty, I believe that being a physiologist trained at the rigorous school of Professor Pompeiano (to which I send thankful thoughts) was also very influential for my research, and that combining my experience in the labs of Carli and Pompeiano has allowed me to work in a wide perspective and through the interdisciplinary approach that I favour.

In conclusion, I feel much in debt to Professor Carli for inducing me—with his peculiar, unshakeable, yet smiling firmness—to choose this line of research that now I find well suited to my attitudes and cultural interests. Giancarlo understood it from the beginning, whereas I took time to realize it. I must thank him not only for being a very supportive tutor, colleague, and friend, but also because he helped me to become a better person, showing that reality, in the lab as in everyday life, is more complex and surprising than one can imagine.

A few years ago I heard him say: ‘I’m involved in highly concrete topics: pain, that nobody knows what it actually is, hypnosis, that might even not exist …’ This seems to me the epitome of his way of getting through life and research; it tells of courage, lightness, and irony.

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GIANCARLO CARLI’S CONTRIBUTIONS TO THE SCIENTIFIC UNDERSTANDING OF HYPNOTIC ANALGESIA

MARK P. JENSEN, PHD

ABSTRACT
This article summarizes one of a number of talks presented at a conference entitled ‘Pain, Hypnosis and Sport Physiology: A Tribute to Giancarlo Carli’, which was held in honour of Dr Carli upon his retirement as a Professor and Chair of the Department of Physiology, University of Siena. Professor Giancarlo Carli is a true Renaissance Man who has developed a translational research programme that spans multiple fields (e.g. hypnosis, pain, exercise physiology), different species (e.g. humans, cats, rats, rabbits), and different foci of study (e.g. behaviour, beliefs, neuroendocrine systems, neuroelectrical responses, brain chemistry). This article reviews his important contributions to just one of these many areas: hypnotic analgesia. His research in this area has shown that: (1) hypnotic analgesia has multiple underlying mechanisms that can impact all components of the pain matrix; (2) individuals with low hypnotic ability can, and do, benefit from hypnotic analgesia treatment; although, (3) individuals with low versus high hypnotic ability display important differences in the neurophysiological and psychological mechanisms underlying hypnotic responding. These critical discoveries have contributed to the scientific understanding of hypnosis and hypnotic analgesia, and also have important practical clinical implications for using hypnosis to treat patients with pain conditions.

Key words: hypnosis, hypnotic analgesia, mechanisms, hypnotic ability, Giancarlo Carli

INTRODUCTION
Professor Giancarlo Carli is a true Renaissance Man. During his productive career, he has developed a translational research programme that spans multiple topic areas (including hypnosis, pain, and exercise physiology), different species (including humans, cats, rats, and rabbits), and different foci of study (including behaviour, beliefs, neuroendocrine system, neuroelectrical responses, and brain chemistry). He is also a gracious host, wonderful mentor, and facilitator of national and international educational events that have contributed significantly to the professional development of other scientists and scientific knowledge.

Just one of the numerous areas he has devoted time to understanding is hypnotic analgesia. His contributions to this field have been many, but three key discoveries and conclusions that he and his research colleagues have made have had perhaps the greatest impact on the field: (1) hypnotic analgesia has multiple underlying mechanisms that can impact all components of the pain matrix; (2) individuals with low hypnotic ability can, and do, benefit from hypnotic analgesia treatment; although, (3) individuals with low versus high hypnotic ability display important differences in the mechanisms that underlie their response to hypnotic treatments.
HYPNOTIC ANALGESIA HAS MULTIPLE UNDERLYING MECHANISMS

In 1998 Professor Carli and colleagues published an important paper examining the effects of hypnotic analgesia on the nociceptive flexion (RIII) reflex in humans, a polysynaptic spinal reflex modulated by supraspinal descending pathways (Danziger et al., 1998). Previous researchers had demonstrated that response to hypnotic analgesia was associated with a reduction in both the somatosensory evoked cortical potentials and in the RIII component of the withdrawal reflex, suggesting that inhibition of nociceptive signals at the spinal level contributed to the efficacy of hypnotic analgesia (Kiernan et al., 1995). Danziger et al. (1998) administered a painful electrical stimulation on the left leg (left sural nerve) to individuals who scored high on the Stanford Hypnotic Susceptibility Scale (SHSS) under two conditions: (1) a control condition and (2) while being given hypnotic suggestions for analgesia. Throughout the procedures, the participants’ pain threshold and physiological responses were assessed. All of the highly hypnotizable subjects demonstrated significant increases in pain threshold and a decrease in the late somatosensory evoked cerebral potential in the hypnosis condition, relative to the control condition. No differences in the autonomic parameters were observed.

What was striking about this study, however, was that all of the participants showed large changes in the amplitude of their RIII reflex, and two clear patterns of changes in this reflex emerged. In 11 of the 18 participants, and similar to Kiernan and colleagues (1995), a strong inhibition of the RIII reflex occurred. However, in the other 7 participants, there was a strong facilitation of the reflex. The findings provided important early evidence that not all highly hypnotizable individuals respond to hypnotic suggestions for analgesia in the same way and that there is not a single physiological mechanism of hypnotic analgesia.

Recent findings have provided a possible interpretation for the unexpected increases in RIII concomitant with decreases in the cortically evoked response to nociceptive stimulation. Specifically, it has been shown that distraction by neutral pictures increases RIII, while increased arousal potentiates the effects of pictures inducing negative emotions on pain and the RIII reflex (Roy et al., 2011). In conclusion, attention and emotion appear to modulate pain through partially dissociable neurophysiological mechanisms (Roy et al., 2011). This may account for the two different RIII modulation patterns seen in the highly hypnotizable subjects described by Danziger et al. (1998); that is, a cognitive style based on distraction (instead of attention to analgesia suggestions) may have induced the increase in RIII observed in a subgroup of highs.

Recently, Giancarlo Carli published an article summarizing two hypotheses that help explain the neurophysiology of pain, and discussed the implications of these hypotheses for understanding hypnotic analgesia (Carli, 2009). The first of these, put forth by Craig (2002, 2003), hypothesizes pain as a homeostatic emotion rather than a simple sensation. As a homeostatic emotion, pain sensations are not only processed in the primary and secondary sensory cortices, but are also processed in multiple areas, including the brainstem (e.g. parabrachial nucleus, which is a primary integration site for all homeostatic afferent activity), diencephalon (e.g. hypothalamus, which organizes goal-directed autonomic, neuroendocrine, and behavioural activity), and telencephalon (e.g. anterior cingular, insular, and prefrontal cortices, which generate representations of self and the meaning of one’s experience). The second hypothesis, put forth by Zimmermann (1979) and Baron and Jänig (in press), argues that some chronic pain conditions involve positive (but maladaptive) feedback loops between efferent and afferent neurons, enhancing their activity, leading to sensory-affective, autonomic, motor, and endocrine abnormalities, and associated chronic pain.
Professor Carli’s important contribution was helping us to comprehend the implications of these neurophysiological models for understanding the effects of hypnotic analgesia on the experience of pain. Specifically, he noted that hypnotic suggestions for analgesia can influence pain through *multiple* mechanisms; via their effects on the initial generation of pain signals (nociception), secondary neuron sensitization, and endocrine/immune responses through the modulation of sympathetic activity. This understanding provides researchers in the field with a wealth of potential targets to examine in the search for neurophysiological correlates of hypnotic analgesia.

The direct clinical implication of Professor Carli’s work in this area is that clinicians should not only target the sensory cortices with their hypnotic suggestions (i.e. they should avoid *only* making suggestions for pain reduction) but rather provide multiple suggestions that impact multiple systems in the pain matrix. Suggestions can, and often should, include those that target the gating mechanisms in the spinal cord (‘... you can filter out any uncomfortable sensations, allowing any and all comfortable and relaxation sensations to grow and expand’), the insula (perception of homeostatic state: ‘... and you feel so comfortable and well, the body is whole’), the anterior cingulate cortex (motivational state: ‘... so there is not really anything you need to do about the pain, you know you are healthy’), and the prefrontal cortex (meaning of the pain: ‘... as you think about your life and what is most important, pain seems to float into the background, because you know that it is possible to live a life consistent with your most deeply held values no matter what else is happening’).

**INDIVIDUALS WITH LOW HYPNOTIC ABILITY CAN BENEFIT FROM HYPNOTIC TREATMENT**

Laboratory research on hypnotic analgesia conducted in the 1960s and 1970s demonstrated a moderate to strong association between the trait of global hypnotizability and response to hypnotic analgesia suggestions (Hilgard & Hilgard, 1975). Perhaps due to this early—and generally consistent—finding, many clinicians believe that only those individuals who have high hypnotic abilities can benefit from hypnosis treatments for pain. However, experimental pain induced in a laboratory setting is not the same as clinical pain experienced by patients in their daily life; the findings from laboratory studies do not necessarily generalize to real clinical settings. Importantly, if these findings do not generalize to clinical populations—that is, if individuals with clinical pain problems who have low hypnotic ability might benefit from hypnotic treatments—and if clinicians screen patients out of hypnotic treatment based on their responses to hypnotizability tests, patients who could benefit from treatment would not be treated. There is therefore a need to test the hypothesized associations between global hypnotizability and response to hypnotic analgesia in clinical populations. Professor Carli and colleagues have examined this important question.

In one seminal study, Carli and colleagues examined the roles that hypnotizability, hypnotic relaxation, and suggestions for analgesia played in the modulation of pain perception in samples of individuals with fibromyalgia (Carli, Biasi et al., 2008). A sample of women with fibromyalgia reporting a pain intensity of at least 50 on a 0–100 visual analogue scale (VAS) were screened for hypnotizability using the Stanford Hypnotic Susceptibility Scale (Form C), and classified as having high (Highs, average SHSS score = 9.57/12) or low (Lows, average SHSS score = 1.22/12) hypnotizability. A sample of healthy controls who were also scored as Lows (average SHSS score = 1.32/12) also participated in the study. Pain intensity was
assessed in the fibromyalgic Highs and Lows at baseline and again following hypnotic suggestions for relaxation (neutral hypnosis) and twice again following hypnotic suggestions for analgesia. The healthy controls (who were Lows) were given the same hypnotic procedures as the patients, although instead of asking them to rate their clinical pain, they were asked to rate the intensity of pain associated with a deep pressure algometer (applied to the foot) that had previously elicited a rating of moderate pain (50/100 on a VAS).

The primary finding from this study was that both of the clinical groups reported reductions in clinical pain following the hypnotic induction and hypnotic analgesia suggestions, whereas the healthy controls who scored low on the SHSS reported no reductions in experimental pain with hypnosis. Interestingly, however, the pattern of pain reductions did differ between the clinical Highs and Lows (see next section on mechanisms of hypnotic responding), with the Lows showing a progressive decrease in pain over the course of the entire session (and a similar response to relaxation suggestions as Highs), while the Highs showed a greater response (than Lows) following suggestions for analgesia.

Although Carli and colleagues’ findings regarding the ability of individuals with low hypnotizability to respond to hypnosis is inconsistent with laboratory hypnosis research, it has been subsequently replicated in other clinical populations (e.g. Butler et al., 2009; Jensen et al., 2009). Thus, even though this might be considered a ‘negative’ finding, it actually raises some very interesting questions that could help us to better understand and explain response to hypnotic treatment. For example, as discussed by Carli and colleagues in a review article on this topic (Carli, Huber et al., 2008), it is possible that having a history of or experiencing chronic pain may facilitate a ‘state’ or states that might increase response to hypnosis. It is also possible that, even if Lows with clinical pain problems can respond to hypnosis—for chronic pain does not differ significantly or substantially between Highs and Lows—the specific strategies used by Highs and Lows to modulate pain in response to hypnotic suggestions differs. For example, Carli and colleagues have suggested that Lows may make more use of relaxation coping strategies than Highs in response to hypnotic suggestions, and the importance of outcome expectancies (i.e. placebo responding) may play a larger role in Lows’ responses to hypnotic analgesia (Carli, Huber, et al., 2008; see also the next section, below). The clinical implications of Professor Carli’s work in this area are clear, however: patients with chronic pain who have low scores on hypnotizability can still benefit from hypnotic treatment, and should not be screened out of such treatment on the basis of such scores alone.

INDIVIDUALS WITH HIGH VERSUS LOW HYPNOTIZABILITY DIFFER IN MECHANISMS OF RESPONSE TO HYPNOSIS

Although the differences between Highs and Lows in global response to hypnotic suggestions appear to be less pronounced (and in some cases, are virtually non-existent) in persons with clinical pain, relative to persons experiencing experimental pain, it remains possible that Highs and Lows differ in their physiological and psychological responses to hypnosis; that is, they may differ in the underlying mechanisms of hypnotic responding. Professor Carli and his colleagues have also made important contributions to understanding differences between Highs and Lows in the way that they respond to hypnotic suggestions.

In one study, for example, two groups of individuals with high and low hypnotizability were asked to stand upright with their eyes closed under three different conditions (presented in
a random order): (1) visual imagery (imagining a scene using visual suggestions); (2) tactile imagery (imagining a scene using tactile modalities); and (3) mental computation (serial subtractions and multiplications) (Carli et al., 2007). Measures included posture, movement/sway, imagery vividness, and effort required by the imagery or mental computation. The Lows rated visual imagery as ‘easier’ than tactile imagery, while the Highs reported that both were easy. Highs also judged the tactile imagery as less effortful and more vivid than Lows. Moreover, the Highs’ body sway was not influenced by the cognitive tasks, whereas the Lows showed task-related changes in body sway. Professor Carli and colleagues concluded that greater attentional availability may be the basis of the absence of cognitive load on postural control in Highs.

In a follow-up study, Professor Carli and colleagues assessed sway, primary sensory modalities used to imagine the absence of perception, vividness of imagery, and effort required by imagery or mental contribution in a group of Highs and a group of Lows while standing with eyes closed under two conditions: (1) suggestions of ‘no perception’ (e.g. ‘... You don’t see and hear anything ... as if your body did not belong to you any more’) and (2) mental computation (serial subtraction and multiplication) (Carli, Manzoni et al., 2008). The results indicated that Highs and Lows differed in their preferred imagery modalities; specifically, 100% of the Lows reported that they preferred a visual modality, whereas both visual and tactile modalities were reported by Highs. Interestingly, no other sensory channel (auditory, olfactory/gustatory) was used as the primary modality during the imagery by any participant. Also, Lows, but not Highs, demonstrated differences in sway during suggestions for decreased sensory availability.

The authors concluded that Highs are able to obtain satisfying mental imagery through both visual and tactile sensory modalities, whereas Lows clearly prefer the visual modality. The difference in the preferred modality of imagery may have been responsible for the difference observed between Highs and Lows in the postural response to vestibular stimulation (Santarcangelo et al., 2010). The earlier component of the vestibular reflex (VR) evoked by electrical stimulation of the labyrinth is not affected by voluntary control; its amplitude depends on the stimulus intensity, and the plane of body sway depends on the position of the head with respect to the trunk. It was found that the plane of body sway during imagery of having the head rotated was the same as it was during real head rotation in Highs, but not in Lows reporting the same vividness of imagery. Interestingly, in order to obtain an experience of ‘head rotated’, almost all of the Highs had chosen the somaesthetic modality of imagery, while all the Lows had chosen the visual one.

This study also confirmed the hypothesis supported in previous studies (Carli et al., 2006) that Highs can translate sensory imagery into real perception, as the earlier component of VR is not affected by voluntariness; this suggests that the response of Highs to suggestions is truly involuntary. However, the greater ability shown by Highs with respect to Lows during attention-demanding conditions like upright stance was not present in sitting subjects (Cavallaro et al., 2010). In these subjects, Professor Carli and colleagues have also reported differences in Highs and Lows in brain activity measures in response to guided visual and somaesthetic imagery tasks. They asked groups of Highs and Lows to experience guided visual and somaesthetic imagery (counterbalanced) on two occasions while semi-reclined. Electroencephalography (EEG) activity during each imagery condition was assessed from 19 electrode sites for all study participants. In this study, there was no difference in preferred imagery modality (visual vs. somaesthetic), vividness, or effort between the Highs and Lows, although both groups reported that visual imagery was more vivid and less effortful than so-
maesthetic imagery. Importantly, EEG activity in response to the imagery condition did differ between groups. Overall, the investigators found a greater distribution of EEG modulation in the Highs (indicating what they called a more 'holistic' brain function), relative to the Lows.

Overall, Carli’s research confirms that the cognitive trait of hypnotizability is highly pervasive and that Highs and Lows differ on some (but not all) important physiological responses to cognitive and physical stimulation. A recent study by Professor Carli and colleagues demonstrated another way that individuals with high hypnotizability differ from those with low hypnotizability. This study compared Highs and Lows with respect to *endothelial dysfunction*, which is a reduction in the ability of the blood vessels to respond appropriately to changes in blood flow. Endothelial dysfunction is also associated with increased cardiac risk (Jambrik, Veneri et al., 2004). Previous research had shown that although mental stress induces endothelial dysfunction, stress-related endothelial dysfunction is lower in Highs than in Lows both at baseline (i.e. not following a hypnotic induction) and after a hypnotic induction (e.g. Jambrik, Santarcangelo et al., 2004; Jambrik, Sebastiani et al., 2005). However, it was not known if painful stimulation also induced endothelial dysfunction and, if so, if either high hypnotizability and/or suggestions for analgesia buffered any effects of painful stimulation on endothelial dysfunction. In this study, a group of not hypnotized Highs and a group of Lows underwent a cold pressor nociceptive stimulation procedure with and without suggestions for analgesia (Jambrik, Santarcangelo et al., 2005). As hypothesized, the investigators found that both Highs and Lows evidenced endothelial dysfunction in response to the painful (pressor) stimulation, but it was much less pronounced in the Highs. The authors concluded that hypnotizability may provide a natural beneficial protection against the vascular effects of acute pain.

In contrast with these clear results on endothelial function, findings regarding possible differences between Highs and Lows in heart rate and heart rate variability (HRV) during the same nociceptive stimulation were not so clear-cut (Santarcangelo et al., 2008). In this second study, a group of Highs and a group of Lows were assessed during five experimental conditions: (1) simple relaxation, (2) painful stimulation (pressure applied at the second costochondral junction via a deep pressure algometer), (3) resting baseline, (4) painful stimulation with analgesia suggestions, and (5) resting baseline. Assessments included pain intensity ratings, respiration rates, heart rate, and HRV. Although Highs reported significantly greater pain reduction than Lows in the hypnotic analgesia condition, relative to the painful condition without hypnosis, the investigators found no group differences in respiration rate, heart rate, or HRV across the different conditions. The authors concluded that HRV may be less responsive to hypnotizability than endothelial function.

Overall, the results of this programme of research suggest that individuals with high versus low hypnotizability differ in some important ways (e.g. with respect to how they process sensory imagery as well as extent of their vascular reaction to pain and stress), but may be similar in others (e.g. cardiac response to pain). Thus, even when hypnotizability does not influence (or has a minimal influence) treatment outcome for clinical pain, it may influence how individuals respond to and use hypnosis for symptom management. The findings support the need to study these potential differences in greater detail. For example, hypnotic protocols for pain management often include suggestions incorporating visual ‘safe place’ imagery for dissociation and deepening the hypnotic experience, coupled with suggestions for changes in sensory experiences, such as morphing uncomfortable (painful) sensations into more neutral and tolerable sensations (e.g. Jensen, 2011). The findings from Professor Carli’s research programme
suggest that an interesting avenue of further research would be to examine the extent to which suggestions for experiencing each sensory modality enhances analgesic effects, and if their relative efficacy differs as a function of hypnotizability.

Also, given the finding that different individuals (even those with high hypnotizability) likely use different cognitive (and associated neurophysiological) responses to hypnosis and hypnotic suggestions, a clear clinical implication of Professor Carli’s research in this area is that hypnotic treatment must be tailored to each patient’s capabilities and responses; one size does not fit all. Although it might be reasonable to begin treatment using hypnotic procedures and suggestions with proven efficacy on average, treatment outcome will likely be maximized if the clinician pays close attention to the patient’s response to each hypnotic suggestion. Future inductions and suggestions should be modified based on the patient’s response during previous sessions (Jensen, 2011).

THANK YOU, PROFESSOR GIANCARLO CARLI

Many people have much to thank Professor Giancarlo Carli for. Scientists should thank him for showing us how to be a modern Renaissance Man—for modelling how to study and understand complex issues from multiple perspectives. Scientists and researchers should thank him for his numerous contributions to our scientific understanding of many fields he has studied, including pain and hypnotic analgesia. Patients with clinical pain problems should thank him for his contributions which have specific important clinical implications that will increase response to treatment. Last, but not least, we all should thank him for being an inspiration and model of generosity, graciousness, and international collaboration. Thank you for your past, current, and future contributions!

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THE HYPNOTIC BRAIN: LINKING NEUROSCIENCE TO PSYCHOTHERAPY

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ABSTRACT

Hypnosis has been an elusive concept for science for a long time. Moreover, the search for objective indicators of the trance state proved to be unsuccessful in the early studies. However, the explosive advances in neuroscience in the last few decades have provided a ‘bridge of understanding’ between classical neurophysiological studies and psychophysiological studies. These studies have shed new light on the neural basis of the hypnotic experience. Conversely, neuroscience research is beginning to consider and use hypnosis as an attractive, viable, and appropriate physiological tool to explore and modulate the cognitive and emotional determinants of complex human experiences. Neuroimaging techniques offer new opportunities to use hypnosis as a probe into brain mechanisms and as a means of studying hypnosis itself.

Furthermore, an ambitious new area of research is focusing on mapping the core processes of psychotherapy and the neurobiology underlying them. Hypnosis research offers powerful techniques to isolate psychological processes in ways that allow their neural bases to be mapped. The ‘hypnotic brain’ can serve as a way to tap neurocognitive questions and our cognitive assays can in turn shed new light on the neural bases of hypnosis. This cross-talk should enhance research and clinical applications.

Key words: hypnosis, psychotherapy, neuroscience, hypnotic analgesia

We carry with us
The wonders we seek without us.

Sir Thomas Browne, Religio Medici (1643)

My personal and professional friendship with Giancarlo Carli dates back to the 1980s. We have shared two major interests through the years: pain and hypnosis. In the pain field, he has been for many of us, including myself, an authoritative master. In the hypnosis field, he was one of the first scientists who, even though not directly involved in hypnotic clinical practice, started to use hypnosis in neuroscience research as an effective and viable tool for scanning the functions of the central nervous system. Because of our converging interests, in 1990 we decided to co-author a comprehensive review on the psychoneurobiology of hypnosis (Seminari sul dolore) (De Benedittis & Carli, 1990), with particular reference to hypnotic analgesia. But foremost he has been a life-long friend to me. And this is the main reason why I wish to celebrate Giancarlo and to say to him: thank you and keep on staying with us!
INTRODUCTION
Hypnosis is the oldest of all psychotherapies and one of the most practised clinical methods for the control of pain. This enviable history denotes and reflects its unsurpassed adaptive power.

In fact, the introduction of hypnosis by Franz Anton Mesmer represented the birth of modern psychiatry in the 18th century. Subsequently, hypnosis earned respect and academic prestige with Charcot, enjoyed widespread popularity with Bernheim and Liebault, and contributed to the birth of psychoanalysis with Freud in the 19th century. But at the dawn of the 20th century, hypnosis seemed to have begun a downward spiral.

In 1912, just before the First World War, which would redraw the political and economic geography and cultural heritage of Europe, Pierre Janet was forced to close his prestigious journal *Revue de l’Hypnotisme* (see Janet, 1923). The last issue bore this epitaph: ‘Hypnosis is dead. At least until it will rise from its ashes’.

It took more than half a century and two world wars until the ‘New Hypnosis’ could rise again, the main actors of this revival, being, among others, Clark Hull, Ernest Hilgard, Martin Orne, and Milton H. Erickson. The innovation introduced by Erickson can be considered as one of the most significant advances of the 20th century in the field of psychotherapy in general and of hypnotherapy in particular.

Despite its unexpected renaissance, hypnosis remained the prisoner of an evil spell. On one hand, it has continued to attract a multitude of weak thinkers and strong and wily spinners, often enhanced and amplified by the media; on the other hand, particularly on clinical grounds, it has struggled between supporters who are sometimes a bit too interested and hypocritical, and snooty detractors often full of prejudices.

But something has changed dramatically in the hypnotic scenario during the last few decades. It is no secret that hypnosis was, and largely remains, a marginal topic in the mainstream of scientific research, mainly because of its empirical and anecdotal approach (often single case reports) and a lack of evidence-based controlled studies. It is true that the absence of evidence is not the evidence of absence (of a given effect), but no discipline can be scientifically recognized in the absence of adequate standards. This also applies to hypnosis.

Moreover, hypnosis has long been an elusive concept for science due to the lack of objective neurobiological markers of the state of trance. But the relentless advances in neuroscience in the last few decades (largely due to the introduction and refinement of sophisticated electrophysiological and neuroimaging techniques) have opened up a ‘bridge of knowledge’ between the classic neurophysiological studies and psychophysiological studies of cognitive, emotional, and sensory systems.

Of course, a bridge is designed to connect two realities bidirectionally. This holds true also for the ‘hypnotic brain’ (De Benedittis, 2006). While recent advances in neuroscience have undoubtedly contributed to unravelling the Veil of Maya of hypnotic reality—that is, its neurocognitive structure (Oakley & Halligan, 2009)—hypnosis is also increasingly being recognized by the international scientific community as a valid and flexible physiological tool to explore the central and peripheral nervous system. This seems to be a real Copernican revolution in the field (De Benedittis, 2004).

Current hypnosis research focuses on two major areas: (a) intrinsic research, that is the research line concerned with the functional anatomy of hypnosis per se, in the absence of
specific suggestions, the so-called ‘neutral hypnosis’ or ‘default hypnosis’ and the neuro-
physiological mechanisms underlying the hypnotic experience in dynamic conditions, and (b) *instrumental research (or extrinsic studies)*, the use of hypnosis and suggestion for studying a wide range of cognitive and emotional processes as well as for creating ‘virtual analogues’ of neurological and psychopathological conditions in order to elucidate their underpinnings and eventually positively change the way we treat them (see Figure 1).

**Figure 1.** Potential domains of the hypnotic brain. Note: altered states of consciousness (ASC), ordinary states of consciousness (OSC).

Let’s now briefly highlight some significant aspects of this epochal revolution, beginning with some recent findings on intrinsic research—what we have learnt from neuroscience on the nature of hypnosis.

**NEUROSCIENCE VS. HYPNOSIS (INTRINSIC STUDIES)**

An important fallout of neuroscience research concerns the precise status of hypnosis: Discrete state of consciousness or process? Reality or hoax?

For a long time hypnosis has been the subject of a quarrel between the dominant ‘credu-
rous’ view (i.e. those claiming hypnosis is an ‘altered state of consciousness’) and the ‘sceptical’
view (i.e. those challenging the existence of hypnosis condition, based on the lack of objective
indicators of trance and the reproducibility of hypnotic effects in a waking state through ap-
propriate ‘motivating suggestions’) (Sutcliffe, 1961; Barber, 1969). This axiological uncertainty
has been widely and definitively overcome by a growing body of convergent neurophysiologi-
cal research—namely electrophysiology and neuroimaging.

The quest for the nature of hypnosis has covered multiple research areas (for a sum-
mary see De Benedittis, 2009): (a) characterizing and validating the hypnotic state/
process, (b) distinguishing altered states of consciousness (e.g. hypnosis, transcendental
meditation) from ordinary states of consciousness, and (c) understanding the
multidimensional neural mechanisms of hypnotic processes and responses (e.g. hypnotic analgesia). There are also clinical implications, such as investigating the neurodynamic correlates underlying hypnotherapeutic strategies and techniques (e.g. direct vs. indirect suggestions; tailored vs. scripted suggestions) and bridging the gap between neuroscience and psychotherapy.

A wide array of novel electrophysiological and neuroimaging techniques have contributed to significant advances in our knowledge of hypnotic phenomena, including functional neuroanatomy of neutral hypnosis. These include electrophysiological studies (e.g. bispectral analysis), neuroimaging (e.g. single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), positron emission tomography (PET)), advanced neuroimaging (e.g. real-time fMRI and brain-computer interface), and neurofeedback.

In particular, recent neuroimaging (fMRI, PET) studies (Maquet, 1999; Faymonville et al., 2000; Rainville et al., 2002; Egner et al., 2005) have contributed to creating a map of regions of interest in the brain during ‘neutral’ or ‘default’ hypnosis (i.e. hypnosis in the absence of any specific suggestion), including the occipital cortex (involved in visualization processing, which is so important for the induction and the experience of hypnosis), thalamus, anterior cingulate cortex (ACC), inferior parietal cortex, and dorsolateral prefrontal cortex. Perhaps we are not far from being able to draw a ‘neurosignature’ (functional neuroanatomy) of hypnosis.

Neuroscience has not only contributed to validating and defining the state of trance; it has also enabled us to differentiate between altered states of consciousness and ordinary states of consciousness. Bispectral electroencephalographic analysis, a sophisticated and complex evolution of spectral analysis, has proved to be effective in differentiating between subjects awake and subjects in trance on the basis of the bispectral (BIS) index (De Benedittis, 2006).

Bispectral analysis utilizes a composite of multiple advanced electroencephalography (EEG) signal processing techniques, including bispectral analysis, power spectral analysis, and time domain analysis. It is a robust aid in monitoring the hypnotic effect of anaesthetics and has emerged as an important tool for anaesthesia management. The BIS index reflects the level of conscious sedation and/or loss of consciousness in patients undergoing general anaesthesia. Bispectral analysis and the BIS index can reliably measure and monitor the depth of hypnotic trance, thus distinguishing the ‘hypnotic zone’ quantitatively and qualitatively from different levels and states of consciousness (De Benedittis, 2006).

For the first time the state of trance can be identified by an objective and reliable (electrophysiological) marker, as compared with the inadequate phenomenological (experiential) and behavioural (measurement scales of hypnotic depth) data of the past (De Benedittis, 2008).

Moreover, recent neuroimaging data suggest a potential anatomical (morphological and volumetric) basis for hypnotizability, linking variations in the rostrum of corpus callosum to differences in attentional and inhibitory processes (Horton et al., 2004).

HYPNOTIC ANALGESIA

A second fruitful area of research has enabled a better understanding of the multidimensional neural mechanisms underlying hypnotic processes and responses—hypnotic analgesia.

One of the oldest medical applications of hypnosis concerns the control of pain, whose effectiveness, known for some time, has only recently found indisputable confirmation at the level of evidence-based medicine in published meta-analyses of randomized controlled studies in both acute and chronic pain (see De Benedittis, 2003, 2004).
Hypnotic analgesia represents a significant paradigm of how neurophysiological and neuropsychological research has contributed decisively to a better understanding of the mechanisms of multidimensional pain control in trance. Since pain has a multidimensional structure involving sensory-discriminative, motivational-affective, and evaluative (attentional) aspects (Melzack & Casey, 1968), it is likely that hypnotic analgesia involves multiple mechanisms of pain modulation.

**SUPRASPINAL CENTRAL MECHANISMS**

One possible explanation for the increased analgesic efficacy of hypnosis in highly hypnotizable subjects as compared with the low hypnotizables is related to greater cognitive flexibility (i.e. the ability to adaptively modify cognitive strategies and awareness) (Crawford & Gruzelier, 1992; Crawford, 1994). In addition, highly hypnotizable subjects possess stronger attentional filtering capabilities and expression of fronto-limbic attentional activities. This allows the subject in trance to be more effective in refocusing their attention and diverting attention away from nociceptive or undesirable stimuli, as well as ignoring irrelevant environmental stimuli (Crawford, 1994).

Cognitive control processes are associated with a supervisory attentional system (SAS), whose activity involves fronto-temporal cortical structures (Shallice, 1988). Neuroimaging techniques (e.g. PET, fMRI, SPECT) have contributed in a decisive way to revealing the putative mechanisms of cognitive modulation of pain, including hypnotic analgesia.

In a pioneering study using SPECT, De Benedittis and Longostrevi (1988) reported a significant decrease of the regional cerebral blood flow (rCBF) in the primary sensorimotor cortex (S1) during suggestions of hypnotic analgesia in highly hypnotizable subjects only, possibly associated with a selective neural inhibition.

But the turning point in neuroimaging studies of hypnotic analgesia was determined by the pivotal studies of a Canadian team headed by Pierre Rainville using PET. In the first of these studies (Rainville et al., 1997), it was shown that hypnotic manipulation of the degree of negative affective resonance (unpleasantness) evoked by a nociceptive stimulation in a group of volunteers concomitantly induced corresponding changes in the activities of the brain structures (i.e. increased/reduced activation of the ACC) involved in coding the motivational-affective component of pain. No change was observed in the activity of the primary sensorimotor cortex (S1) involved in processing the sensory-discriminative component of the nociceptive stimulus (Rainville, Carrier et al., 1999; Rainville, Hofbauer et al., 1999). The extraordinary selectivity of hypnotic suggestion to manipulate differentially the two main components of the painful experience was documented by a striking linear correlation between the intensity of negative affective resonance, as suggested in hypnosis, and the level of activation of the ACC.

This pioneering study was followed by others of the same group and by Belgian researchers (Faymonville et al., 2000; Hofbauer et al., 2001), which confirmed and extended the results of the aforementioned study, suggesting that the ability of hypnosis in differentially modulating the different aspects of pain perception is not rigid, structural, and unidirectional, but dynamic and dependent upon the structure and formulation of hypnotic suggestions.

Contrary to what had been previously believed (De Benedittis et al., 1989; Hilgard & Hilgard, 1994), it is becoming increasingly clear that hypnosis can modulate effectively not only the motivational-affective component of pain but also the sensory-discriminative one.
(more directly linked to the intensity of the nociceptive stimulation), albeit to a lesser extent. These findings confirm the great cognitive-perceptual flexibility mediated by trance and will certainly exert a significant impact in the clinical context.

**SPINAL MECHANISMS**

Hypnotic analgesia may also depend on the activation of descending inhibitory systems (descending noxious inhibitory controls (DNIC)) that specifically modulate the spinal transmission of the nociceptive input. The involvement of these systems during hypnotic suggestions of analgesia has been demonstrated by electrophysiological studies that have documented that hypnosis significantly reduces the amplitude of the nociceptive flexion reflex (R-III), believed to be linearly related to the intensity of perceived pain (Kiernan et al., 1995; Danziger et al., 1998). The effect was proportional to the level of hypnotic suggestibility.

**AUTONOMIC AND PERIPHERAL MECHANISMS**

In addition to the spinal and supraspinal mechanisms, there is increasing evidence that hypnosis also modulates the activity of the autonomic nervous system (ANS) and peripheral nervous system (PNS). The sympatho-vagal interaction of ANS during trance was analysed for the first time with spectral analysis of the heart rate variability signal (RR interval) by De Benedittis and colleagues (1994). The study showed that hypnosis modulates the RR interval by shifting the balance of sympato-vagal interaction towards an increased parasympathetic output, concomitant with a reduction in the sympathetic tone. The effect is positively correlated with hypnotic susceptibility. These data are of particular interest in the modulation of pain because the autonomic output may induce, exacerbate, or prolong pain (e.g. in complex regional pain syndromes).

Finally, Langlade and colleagues (2002) have shown that the heat pain threshold assessed by thermal stimuli was significantly elevated during hypnosis. These findings, if confirmed, would indicate that hypnosis can down-regulate neuronal inflow from A delta and C fibres stimulation, possibly explaining, at least partially, the analgesic effect.

In conclusion, recent studies on hypnotic analgesia are remarkably convergent and suggest that the concomitant activation of a specific peripheral and central neural network, structured in a hierarchical multiple and flexible organization (Price, 1999), might represent the ‘neurosiness’ of the hypnotic modulation of pain (De Benedittis, 2003). It is noteworthy that the structures involved in pain perception are the same as those involved in its cognitive, hypnotic modulation (Peyron et al., 2002). However, the functional dynamics of these complex patterns remains to be further elucidated.

**HYPNOSIS VS. NEUROSCIENCE (INSTRUMENTAL STUDIES)**

**COGNITIVE MODULATION**

Neuroscience has begun to consider using hypnosis as a viable physiological tool to explore and modulate the emotional and cognitive determinants of human experience. Hypnosis can be considered as a heuristic paradigm of cognitive modulation (De Benedittis, 2009). Potential domains of current and future research include: attentional processes, pain control, manipula-
tion of mental images and perceptual processes, mnestic processes, exploration of conscious and unconscious processes, neurocognitive processes, and genetic determinants of hypnotic responsiveness (as part of the Human Genome Project).

VISUAL AND AUDITORY PERCEPTION
In addition to pain perception, the ability of hypnotic suggestions to modulate other perceptions has been investigated in several neuroimaging studies. One study on hypnotic suggestions of auditory hallucinations (Szechtman et al., 1998) has shown that the brain areas activated are essentially the same during the actual perception of an auditory stimulus (albeit with a gradient of less intensity of activation). Similarly, Kosslyn and colleagues (2000) have shown that visual illusions under hypnosis activate visual associative areas similar to those activated when perceiving a real visual stimulus. These studies suggest that the line between real perception of a stimulus and distorted perception (i.e. illusion) or absence of a stimulus (i.e. hallucination) is more elusive than formerly believed.

According to Mountcastle (1978), the neuron is a storyteller and the relationship between reality and brain is isomorphic and analogic—like the (approximate) relationship between a map and the territory it represents.

SENSORY HALLUCINATIONS
Derbyshire and colleagues (2004) have used hypnotically suggested pain in normal pain-free individuals to create an unequivocal analogue of functional pain. They found that the hypnotic pain experience was associated with widespread activation in classic pain areas (thalamus, anterior cingulate cortex, insula, prefrontal cortex, and parietal cortex), similar to that seen with a comparable physically induced pain and proportionate to the level of subjective pain reported. Interestingly, this activation pattern was not seen when participants were asked to imagine the same pain experience.

MOTOR HALLUCINATIONS
Motor control hallucinations are common in schizophrenic, dissociative, and conversion disorders. Blakemore (2003) studied eight highly hypnotizable subjects using PET. Three experimental conditions were included in the study: active movement (AM), real-passive (RP) movement, and hypnotic deluded passive movement (DP). Results showed an increased activity in the parietal cortex and cerebellum in the DP condition, with an activation pattern similar to that detected in the AM condition.

HYPNOSIS AND ATTENTION
Modern cognitive studies have suggested that attention is neither a property of a single brain area nor that of the entire brain. Attention can be viewed as involving a system of anatomical areas consisting of three more specialized networks. These networks carry out the functions of alerting, orienting, and executive control. Distinct brain areas mediate different attentional processes (Raz & Shapiro, 2002; De Benedittis, 2003).

Neuroimaging studies suggest that discrete brain areas mediate specific attentional processes. In a recent study (Raz et al., 2002) the Stroop interference test was used to assess interference in cognitive attentional processes under hypnosis. In more complex tasks, highly
hypnotizable subjects showed significantly shorter reaction times compared to low hypnotizable subjects, confirming a greater attention skill related to high hypnotic susceptibility.

**HYPNOSIS AND MEMORY**

It is well known that hypnosis is effective in inducing post-hypnotic amnesia and modulating implicit and explicit mnestic content (Cox & Bryant, 2008). A recent neuroimaging study (Mendelsohn et al., 2008) has shown that the suppression of episodic memories in hypnosis (post-hypnotic amnesia) is associated with changes in brain areas responsible for long-term recall (i.e. occipital cortex, temporal cortex, and prefrontal cortex). These data have been interpreted as evidence of an active inhibition of the processes of mnemonic recall.

**EXPERIMENTAL NEUROPSYCHOPATHOLOGY AND NEURODYNAMIC CORRELATES OF THERAPEUTIC TECHNIQUES**

Experimental neuropsychopathology is aimed at elucidating the neurocognitive processes that contribute, in whole or in part, to the aetiology, exacerbation, or maintenance of abnormal behaviour (Zvolensky et al., 2001).

Hypnotic suggestions can serve as an experimental tool for the creation of hypnotic clinical analogues (virtual patients) (Oakley & Halligan, 2009) of neurological or psychiatric diseases, in order to elucidate psychophysiopathological mechanisms and eventually being used appropriately in the therapeutic setting.

The most fascinating and advanced frontier is represented by the use of hypnosis as a neuropsychobiological investigation tool in psychotherapy (e.g. assessing psychobiological correlates of experimental unconscious conflicts with electrophysiological and/or neuroimaging techniques).

**HYPNOTIC ANALOGUES OF NEUROLOGICAL AND/OR PSYCHIATRIC CONDITIONS (VIRTUAL PATIENTS)**

An intriguing study by Halligan and colleagues (2000) generated a hypnotic analogue of conversion hysteria (i.e. limb paralysis) in a healthy subject and compared his fMRI with those from real patients with hysteria. The results were striking: in the virtual patient the same key targets were activated as those observed in real patients.

The psychophysiological and behavioural changes observed during the recall of memories in patients who have suffered psychological trauma often resemble the phenomena observed in trance. Activation of identical brain structures has been observed in studies of strong emotional recall as well as in studies of neuroimaging in hypnosis: thalamus, hippocampus, amygdala, medial prefrontal cortex, anterior cingulate cortex (Vermetten & Bremner, 2004). Therefore, it is not unlikely that the neurodynamic circuits activated in the recall of traumatic memories in patients with post-traumatic stress disorder largely overlap with those observed in trance for the recovery of unconscious memories/conflicts.

**HYPNOTIC MODULATION OF CONFLICTS IN THE HUMAN BRAIN**

Increasing evidence suggests that cognitive-emotional conflicts involve the activity of the ACC. Hypothesizing that such conflict reduction would be associated with decreased ACC activation, Raz and colleagues (2005) recently combined neuroimaging methods and studied...
highly and less hypnotizable participants both with and without a suggestion to interpret visual words (i.e. Stroop interference test) as nonsense strings. The associated increase in ACC activity in the absence of compensatory changes in left frontal cortical areas has been interpreted as evidence that hypnosis acts to decouple the normal relationship between conflict monitoring and cognitive control.

HYPNOSIS: QUO VADIS?

New and more demanding challenges will be faced to further elucidate the relationships between hypnosis and neuroscience. Many crucial questions need to be answered. First, how different brain structures are involved and interact with each other in trance. Second, we need to develop new heuristic experimental paradigms that address the different aspects of hypnotic processes/responses (De Benedittis, 2003).

Furthermore, it is of paramount importance to evaluate those factors that mediate the trance state (De Benedittis, 2003): (a) the structure of hypnotic suggestions (e.g. direct vs. indirect; standard vs. custom), (b) suggestion processing, (c) the role of cognitive variables (such as attention/inattention), (d) differential effects of hypnosis on cognitive-affective dimensions, (e) the role of the hypnotic relationship, and (f) the psychosocial context.

Recent studies (Barabasz & Barabasz 2006; Barabasz & Christensen, 2006) have assumed the superiority of customized hypnotic induction and suggestions (tailored) vs. standard induction and hypnotic suggestions in patients with irritable bowel syndrome and in patients undergoing age regression.

Finally, the question of the alleged superiority of indirect vs. direct hypnosis still remains unsolved. The superiority of indirect techniques is based upon Erickson’s assumption (Erickson & Rossi, 1979) that these techniques bypass resistances in resistant patients. Experimentally, there is no evidence for this assumption: the more resistant subjects do not differ from those less resistant (therapeutic reactance scale) (Matthews et al., 1985; Lynn et al., 1993; Groth-Marnat & Mitchell, 1998). On clinical-experimental grounds, no difference in hypnotic pain relief between direct and indirect suggestions could be found in the only published study (Maurer et al., 1993).

CONCLUSIONS

Hypnosis is no longer a matter of dispute and controversy in the international scientific community. It has not only been established as a viable, valid, and reliable intervention for controlling discrete clinical syndromes, but it has been eventually recognized as a real psychobiological state and process. Mostly important, neuroscience research is beginning to consider and use hypnosis as a physiologically effective tool for studying the normal human brain and to investigate neurodynamic correlates of psychotherapy (De Benedittis, 2003). Also, hypnotic clinical analogues are increasingly serving as clinical simulations to investigate specific hypotheses concerning neuropsychopathological disorders.

In conclusion, the most recent clinical-experimental paradigms have established the role of the hypnotic brain as a physiological probe to explore brain/mind mechanisms, producing, in turn, an important impact on the advances of our knowledge on the nature of trance. This seems to be a new callisthenics for the human brain/mind.
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MOBILIZING HYPNOTIC ABILITY TO COPE WITH PAIN: A CONVERSATION BETWEEN BASIL FINER AND MARK P. JENSEN

BASIL FINER, MD AND MARK P. JENSEN, PHD

ABSTRACT

This article summarizes the key points of a conversation between Basil Finer and Mark P. Jensen in which Dr Finer discussed his thoughts about hypnosis and hypnotic analgesia with respect to the work of Giancarlo Carli. These ideas were also expressed during a conference entitled ‘Pain, Hypnosis and Sport Physiology: A Tribute to Giancarlo Carli’, which was held in honour of Dr Carli upon his retirement as a Professor and Chair of the Department of Physiology, University of Siena. Dr Finer begins by discussing how his research in the neurophysiology of hypnosis overlaps with Dr Carli’s research interests. Dr Finer goes on to describe how his training as an anaesthesiologist informed his clinical practice and research programme. He notes that Dr Carli’s work in the area of animal hypnosis has important practical implications for easing suffering in patients. Dr Finer concludes by describing a number of cases in which he found hypnotic analgesia to be particularly helpful, and noting some of the more exciting new trends in hypnosis research.

Key words: hypnosis, hypnotic analgesia, Giancarlo Carli

Mark Jensen: When did you first meet Dr Carli?

Basil Finer: I first met Giancarlo Carli at the 2nd International Association for the Study of Pain Congress in 1978, but had the opportunity to have more interaction with him when he was the Organizing Committee Chairman for the 3rd European Congress of Hypnosis in Psychotherapy and Psychosomatic Medicine in Abano Terme (Padua), in 1984. He had obtained some research training in neurophysiology in the USA, and continued a programme of neurophysiological and neuropharmacological research on animal and human hypnosis here in Italy (Carli, 1982). He was interested in the human hypnosis research studies that I was engaged with, alongside neurophysiologists K. E. Hagbarth on spinal reflexes (Hagbarth & Finer, 1963), R. G. Hallin and H. E. Torebjörk on sympathetic reflexes (Finer et al., 1978), K. Graf on blood flow in skin and muscle (Finer & Graf, 1968), and G. Aschan and K. E. Hagbarth on nystagmus reflexes (Aschan et al., 1962) at the University Hospital in Uppsala. He was also interested in our work on physiological changes during minor surgery under hypnotic analgesia at Samariterhemmet Hospital in Uppsala (Finer et al., 1973). On one occasion he helpfully looked through a lecture I was to give. Later, he kindly invited me to lecture on this research here in Siena. He was a
A CONVERSATION BETWEEN BASIL FINER AND MARK P. JENSEN

MJ: Can you talk a little about your training and first experiences with the use of hypnosis.

BF: I am a retired anaesthetist and pain treatment specialist. I have been using hypnotic techniques as a supplement to physical and pharmacological techniques for helping people cope with persistent pain for over 50 years. I am affiliated with the Pain Centre at the University Hospital in Uppsala, Sweden. I have been involved in a number of research projects studying hypnosis and hypnotic analgesia over the years, and am currently involved in a research project, together with my colleague Dr Aida Plesan, on the use of hypnotic techniques for helping patients manage the pain associated with burn injuries. In 1947, while still a medical student in London, I learned to use progressive relaxation (Jacobson, 1938; Dick-Read, 1943) as well as pharmacological agents for obstetric pain. I also learned group therapy strategies (Foulkes, 1948) and the use of social clubs (Bierer, 1944) and pharmacological agents for rehabilitation.

In 1949, during my anaesthetic training, I learned that all anaesthetic agents have advantages and disadvantages, and that the art of anaesthesia was to provide the treatment(s) that provide the maximum of advantages and the minimum of disadvantages for the patient and procedure in question (Ostlere, 1949). I also learned that some of the most important elements for achieving an effective anaesthetic induction included a good trusting relationship between anaesthetist and patient, especially with children, and that an experienced technique with intravenous needle, local anaesthetic needle, and/or mask produced better operative conditions and a faster, calmer recovery. In addition, if repeated procedures were indicated, good memories from the previous meetings made treatment easier. As I later learned more about the use of hypnosis for pain management, I came to understand that these procedures seemed to mobilize some basic hypnotic ability.

In 1952, I saw a demonstration of pain relief in a patient with severe burns with hypnotic analgesia by Dr Albert Mason (1960). This confirmed for me the value of psychological as well as physical methods for pain relief. Three years later I participated in a training course run by the British Society for Medical and Dental Hypnosis, facilitated by Mason. That same year, the British Medical Association recommended the routine teaching of medical hypnosis in medical schools in Great Britain. In 1958, the American Medical Association did likewise.

MJ: Have you had any experience with animal hypnosis?

BF: In 1958, when I was working as an anaesthetist in Östersund, Sweden, one of my surgical colleagues Dr (later Professor) Willem van den Linden was studying the artificial formation of gallstones in guinea pigs. He anaesthetized them with diethyl ether, opened the abdomen, inserted sterile suture material into the common bile duct, resutured the abdomen and allowed them to waken. Diethyl ether anaesthesia has four stages: analgesia, excitation, surgical anaesthesia, and respiratory paralysis (Guedel, 1937). In guinea pigs, the excitation stage is violent. I was allowed to use animal hypnosis (Völgyesi, 1966)—one of the many areas where Giancarlo Carli has made numerous and
important contributions (e.g. Carli, 1982)—on these animals before they were anaesthetized. I put them on their backs and stroked them for some minutes on their abdomens. When they had been aroused, they were then anaesthetized in the usual way with diethyl ether. What we found was that the excitation stage was much calmer and shorter than with the control animals without animal hypnosis. These strategies seemed to mobilize some basic hypnotic ability in the guinea pigs and might be (and probably should more often be) used for helping animals experience less suffering during medical procedures.

I have noted a similarity between animal hypnosis and the natural calming that can occur in human infants. When allowed, new-born infants often actively crawl to the mother’s breast and start rooting for and sucking at the nipple. This attachment (Bowlby, 1972) movement is purposeful and adaptive. It relieves hunger and restores homeostasis via negative feedback (Pickering, 2010). When new-born infants require blood tests, it is usual to make a puncture in the heel. This is painful and the infants usually withdraw the foot and cry. However, if the mother is breastfeeding them during the heel puncture, they evidence much less pain (and suffering) behaviour. Thus, these strategies appear to mobilize some basic hypnotic ability in new-born infants.

Remembering my work in animal hypnosis, in 1961 I was asked to anaesthetize a 1-year-old boy to make a change in the plaster casts on his congenitally dislocated hips easier. Prior to the procedure, I found him standing in his cot and screaming, probably because he had become afraid from previous anaesthesias. I stroked him on his back and spoke gently to him with positive encouragement. He calmed down and was subsequently successfully anaesthetized without fear. These strategies seemed to mobilize some hypnotic ability in this little boy.

Part of my interest in this area may have come from my own experience of pain as a child. Pain has been defined as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (Merskey, 1986). In an explanatory note to this definition of pain, Merskey wrote: ‘Each individual learns the application of the word through experiences related to injury in early life.’ This has been so in my own life. In 1927, when I was 1½ years old, I had a bilateral middle-ear infection, which was very painful. Seven years later, in 1935, and when I was 9 years old, my left ear was still infected, and so I underwent a mastoidectomy operation. The day after the operation, the dressing in the open wound was changed and a new dressing inserted.

At the time, the pain I experienced with this wound change was not only a signal of tissue injury, but was also intolerable. It was far more than I could ever have imagined prior to this experience. It would be 10+++ on the typical 0–10 scale. As might be expected, I exhibited extreme pain behaviour. Rather than being soothed and calmed, however, I was blamed for being uncooperative and not being able to control myself. I was told to lie still and be quiet. I can still remember the feeling of shame.

My early experience with nociceptive pain has contributed to my subsequent interest in coping with pain. In our research study (Hagbarth & Finer, 1963), we compared the withdrawal response of subjects following either (1) electrical shocks administered randomly by a colleague versus (2) similar intensities of electrical shocks adminis-
tered by oneself. Consistent with our hypotheses (and my personal experience), shocks administered randomly by others are more difficult to cope with and produce much stronger withdrawal responses than similar shocks released deliberately by oneself.

*MJ:* What are some of the more interesting recent research findings regarding pain and hypnosis?

*BF:* In the long list of scientific papers by Carli and his associates in recent years, some subjects of importance have been muscle function and balance in relation to hypnotizability in athletes and in patients with fibromyalgia. It has recently become possible to localize cerebral changes associated with the respective sensory and emotional components of persistent pain with imaging techniques (Rainville & Price, 2004). It has also been shown that hypnotic analgesia reduces the unpleasant emotional component more than the sensory component of pain (Kiernan et al., 1995). People with persistent pain often experience their pain as an enemy within their own bodies, contributing to a disintegration of their normal, healthy, physical and cognitive, cybernetically organized self-control systems (Wiener, 1948; Pickering, 2010). This can result in feelings of inner chaos (Gleick, 1988), helplessness (Seligman, 1975), loss of self-esteem (Elton et al., 1978), and life crisis (Finer & Melander, 1985), which they are unable to overcome. These feelings may well be strengthened by aversive comments from family, friends, working colleagues, medical care professionals, and insurance professionals, greatly reducing their coping abilities. Although pharmacological agents can be important in pain treatment, they rarely if ever relieve pain completely (there is no such thing as a 'pain killer'), and their side-effects can sometimes seriously impair other bodily functions and increase the suffering (Rhodin, 2010).

*MJ:* How do you see yourself as a clinician treating pain?

*BF:* My function is to use myself (Balint, 1957) as an encouraging catalyst in this cybernetic system, communicating (Barnes, 2002; Fjeldstad, personal communication, 2010) with patients who have a 'normal hypnotic ability' to teach them to use their own hypnotic skills to achieve relief from pain. With these skills, they can actively use the mind’s capability for change (i.e. 'plasticity'; Hagbarth & Finer, 1963) and adaptability (Pickering, 2010) to overcome inner chaos, recover self-esteem, and more effectively cope with the changed quality of life triggered by persistent pain. This communication could be described as a circular change in the 'news of differences that make a difference' (Bateson, 1972) from an unacceptable level of pain and suffering to an acceptable level of pain and suffering, involving both the observed and the observer.

I work on the assumption that much of the severity of persistent pain is due to negative learning. My aim as a hypnotherapist is to act as a catalyst, encouraging and motivating patients to find and mobilize their own hypnotic ability, using relaxation and positive imagination, both for physical and mental functions. Thus, my patients are helped to self-help and build their self-esteem, self-confidence, self-encouragement, and self-reliance. They learn to use both the healthy and the unhealthy parts of their body and suitable pharmacological agents (with self-hypnosis, these can be prescribed
in reduced doses) to strengthen the battle against our common enemy—persistent pain.

Mesmer (1734–1815) was condemned by the Royal Commission in Paris in 1784 because they determined that the scientific basis of his ‘animal magnetism’ therapy was not in fact magnetism (Bailly, 2002). Instead, they determined that the patients actually did improve, but did so as a result of their own imagination. The Commission also recommended that these responses to imagination be studied further. Unfortunately, these recommendations took another 200 years to be acted upon. However, the worldwide use of research and literature on medical, dental, and psychotherapeutic hypnosis bear witness to the value of hypnotic techniques in helping patients with persistent pain (Hilgard & Hilgard, 1975; Jensen, 2010).

Ever since I first saw a demonstration of hypnotic techniques for reducing the pain of burns in 1952, I have learned, heard, and read about giving ‘suitable suggestions under hypnosis’. Both Braid (1843) with Neurypnology and Bernheim (1886) with La Suggestion removed the focus from ‘mesmeric passes’ to ‘suggestion’. Even Weitzenhöfer and Hilgard’s Stanford Scale for hypnotizability (1959) and other later scales use test responses to standard suggestions. In Hilgard’s laboratory, Bányai (1976) showed that during exercise (on a stationary bicycle), suggestions could induce hypnosis just as effectively as when they are administered during relaxation. Erickson described the subject’s spontaneous learning ability in hypnosis, communicating with the ‘unconscious’ (Erickson, 1967). It has also been shown that suggestions with hypnosis are more therapeutic than suggestions without hypnosis (Frenay et al., 2001).

When people with persistent pain consult me, I find it very difficult to provide ‘suitable suggestions under hypnosis’. We do not know each other, so how can I know which suggestions are most ‘suitable’? How do I know that my ‘suitable suggestions’ will not be experienced negatively by these people? Instead, I start by asking them how the pain has changed their lives. This gives me an idea of what they were like when they were healthy, with self-control and self-esteem, with details of how they enjoyed family, friends, working environment, and strong interests. In addition, by asking such questions, they come to understand that I am interested in them as people. This increases the therapeutic trust, which is paramount to effective hypnotherapy. Together, we can discuss which positive experiences they have had during their lives and their natural creativity.

During relaxation, I can then encourage them to imagine and concentrate on the positive experiences of their own choice. I invite them to imagine that the soles of their feet become less sensitive to touch, testing for changes in the plantar reflex (Finer, 1965). Similar procedures can be used for abdominal reflexes, eyelash reflexes, and throat reflexes. People who have sensitive reflexes are often amazed that they are able to gain control over their reflex responses. Then, I usually invite them to imagine their bodies so light that they can get up and walk about, with eyes open, still completely relaxed. Sometimes they are completely free of pain at this point, just while they are walking about. Then they relax with eyes closed and positive imaginative experiences. When they open their eyes again, we can discuss their experiences during relaxation, so that I can get feedback for our continued collaboration. These abilities to change their
pain sensitivity at will are most encouraging, so that they can begin to regain their self-control and self-esteem.

MJ: Would you describe some of your cases where you found hypnotic analgesia to be particularly helpful.

BF: In 1959, I was asked to anaesthetize a 21-year-old man for debridement of 40% body surface burns and skin transplantation. Two weeks previously, he had developed cardiac arrest during anaesthesia. He was resuscitated but the operation was abandoned. When I met him in the ward, he refused a new anaesthesia, fearing that, this time, he might die. Local analgesia was impossible because of the size of the injured areas and risks of infection.

Encouraged by Mason (1960) and Crasilneck and colleagues (1955), I helped him to mobilize his (motivated) hypnotic ability to produce analgesia, and he was successfully operated on five times, using only his hypnotic analgesia (Finer & Nylén, 1961). One year later, he was re-admitted for revision of his scars under local analgesia. Afterwards, I asked him why he did not use his hypnotic ability again. He replied that he was no longer afraid of dying during the operation, and that he was no longer motivated to use hypnotic ability because it required too much concentration!

In 1988, a 40-year-old woman with pelvic girdle pain following two pregnancies, unrelieved by orthopaedic insertion of metal plates in the pelvis, was referred for pain relief. She described her pain experience as ‘torture’ and explained that she had spontaneously developed a technique of ‘taking myself out of my body, so that I don’t feel the pain’. This was a classic example of dissociation and is often found in torture victims (Westin, 1991).

In 1991, a 12-year-old boy with pseudo-tumour cerebri was referred for relief of neuropathic pain in the abdomen, following an unsuccessful cerebrospinal shunt operation to reduce the raised pressure of the cerebrospinal fluid. During training with hetero-hypnosis and then with self-hypnosis, he has been able to cope with the neuropathic pain, though it has not disappeared, and many shunt complications necessitated repeated surgical interventions. In his school for handicapped children, he uses his self-hypnosis for all new learning situations and finds that with this he learns much faster than he could previously or than his school colleagues can learn now. This suggests that by mobilizing his hypnotic ability, he has been able, spontaneously, to reduce previous inhibitions and, thereby, increase his learning ability.

MJ: Any final thoughts about hypnotic analgesia?

BF: I was amused and stimulated by Carli’s words included in the invitation to this meeting in his honour: ‘I’m involved in highly concrete topics: pain, that nobody knows what it actually is, hypnosis, that might even not exist ...’. In addition to honouring Carli’s prolific and valuable scientific output, my clinical contribution has been to emphasize the subject’s inherent hypnotic ability or talent, which, among the various available methods for coping with pain, can be encouraged and developed by the experienced therapist. In everyday life, access to basic homeostatic mechanisms, physical and cognitive, which I would call ‘hypnotic abilities’, can be achieved by inducing trance states (Tart, 1969).
In my view, negative learning experiences, from birth onwards, can diminish access to these hypnotic abilities in people with persistent pain. Progressive relaxation and positive imagination can help facilitate a re-learning of these and allow therapeutic access to these abilities.

In 1964, an American psychologist, named Mowrer, wrote a book called The New Group Therapy, in which he asserted that alcoholics were better helped by trained former (or sober) alcoholics than by doctors and psychologists (Mowrer, 1964). This gave me the idea of having trained former pain patients (pain people) as valuable specialists in a multidisciplinary pain clinic. Thus, in our multidisciplinary pain clinic at Samariterhemmet Hospital, Uppsala, individual and group hypnosis and self-hypnosis were integral parts of the treatment programme (Finer, 1982), with pain people as co-therapists.

One area of study that I am also very interested in is the genetics of hypnosis. One of the research areas at the Pain Centre in Uppsala, led by Professor Torsten Gordh, is a search for genetic and local tissue factors that might be associated with the development of persistent pain. Recently, a Special Interest Group within the International Association of Pain has been formed to facilitate research into genetic factors in people with persistent pain. It seems to me worthwhile searching for genetic and tissue factors in hypnotic ability, both in healthy and unhealthy individuals, and in their families, and particularly in people with persistent pain.

Dear Giancarlo—thank you for your life-long work and accomplishments in helping to lighten the darkness around pain and hypnosis, thereby reducing academic scepticism and encouraging much more widespread use of hypnosis in coping with pain.

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