

HYPNOTIZABILITY AND CHRONIC PAIN: AN AMBIGUOUS CONNECTION

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Abstract

We discuss the role of hypnotizability in the development and treatment of chronic pain, and in the prognosis of its possible cardiovascular consequences. Data indicate that high hypnotic susceptibility is not necessary for the relief of chronic pain obtained through hypnotic treatment. Moreover, and at variance with an earlier hypothesis, being highly susceptible to hypnosis does not represent a higher risk for developing chronic pain; in addition, high hypnotizability may be a favourable protective factor against the possible cardiovascular consequences of chronic pain. However, we cannot exclude that psychological factors such as mindfulness, well-being and pain-catastrophizing differ in 'Highs' versus 'Lows', and these may represent the real agents of the differences between the two groups in pain experience, the development of chronic pain, and possible vascular consequences of chronic pain. Copyright © 2008 British Society of Experimental & Clinical Hypnosis. Published by John Wiley & Sons, Ltd.

Key words: cardiovascular risk, chronic pain, hypnotizability, pain dimensions

Chronic pain, that is pain lasting for more than 3–6 months (Merksey and Bogduk, 1994), is a major public health concern due to its physical, psychological, economic, and social impacts on patients, their families and society (Brennan et al., 2007). In the US, the cost of lost or 'reduced effectiveness' workdays due to chronic pain has been estimated at US \$50–70 billion per annum (Steward, Ricci, Chee, Morganstein and Lipton, 2003). In Europe, nearly 20% of adults suffer from one or more chronic pain conditions (Breivik, Collett, Ventafridda, Cohen and Gallacher, 2006), with back pain, recurrent headaches and arthritis among the most frequent (Bonica, 1990). Due to its wide-ranging consequences, which include marked changes in the behaviour, functioning and overall life perspective of the patient, chronic pain has been acknowledged as a disease in its own right (Niv and Devor, 2004). In addition, it is associated with increased susceptibility to other diseases due to its effects on the immune system (Machelska, Mousa and Stein, 2001; Niv and Devor, 2004) and with an occurrence of 13.6% of coronary disease as compared to 6.5% in matched subjects not suffering from chronic pain (Berger, Dukes and Oster, 2004).

A primary issue regarding our understanding of pain concerns the progress from acute to chronic pain. This progression may occur via changes in complex neural mechanisms at both peripheral and higher central levels. For example, inflammation caused by a tissue lesion activates nociceptors and produces two different phenomena – acute pain and hyperalgesia, i.e. increased sensibility for subsequent noxious stimuli (Jessell and Kelly, 1991). Hyperalgesia usually persists even after the pain has disappeared and can

facilitate future pain episodes. Repeated injuries or inflammation exacerbate both mechanisms and can eventually lead to a chronic pain syndrome, which may persist even when the initiating medical condition has resolved (Cohen, 2004; Niv and Devor, 2007). Autonomic nervous system dysfunction may also contribute to sensitization and the development of chronic pain (Baron, Lavigne and Fields, 1999). In fact, sympathetic overactivity (often associated with sympathetic hypoactivity in response to stressors) or parasympathetic underactivity, mostly measured by spectral analysis of heart rate variability, has been reported by several studies in fibromyalgia (Martinez-Lavin and Hermosillo, 2000), irritable bowel syndrome (Heitkemper, Jarrett, Cain, Burr, Levy and Feld, 2001), chronic fatigue (Pagani and Lucini, 1999) and restless legs syndrome (Sforza, Pichot, Barthelemy, Haba-Rubio and Roche, 2005).

On the other hand, affective disorders, such as major depression, play an important role in the experience of chronic pain. At the same time, depression can impact the development and/or persistence of pain symptoms (Currie and Wang, 2005). In contrast, subjective well-being, a sense of happiness and satisfaction with the various domains of one's own life, including those unrelated to health, may act as a buffer or source of 'resilience' (Karoly and Ruehlman, 2006) against depression and other negative emotional consequences of chronic pain (Cummins, 2000; Chow, Lo and Cummins, 2005) and may therefore positively influence the prognosis of the disease.

Also cognitive characteristics, such as coping styles and *pain catastrophizing*, that are known to be relevant for the general quality of life of patients with chronic pain and for the prognosis of the disease, may be important in the development of chronic pain (Keefe, Rumble, Scipio, Giordano and Perri, 2004). In particular, pain catastrophizing, a cognitive tendency to (mis)interpret pain as extremely threatening and to dwell on the most extreme negative consequences of pain, has emerged as one of the most important cognitive modulators of pain perception, accounting for 7% to 31% of the variance in pain ratings (Geisser, Robinson, Keefe, Weiner et al., 1994; Sullivan, Thorn, Haythornthwaite, Keefe, Martine, Bradley and Lefebvre, 2001). During an acute pain episode (e.g. low back pain), this tendency can promote fear of movement-related pain and consequent disuse, which can then in turn lead to disability and depression and finally may contribute to the development of a chronic pain disorder (Leeuw, Goossens, Linton, Crombez, Boersma and Vlaeyen, 2007). On the contrary, *pain acceptance*, that is an active willingness to engage in meaningful activities in life regardless of the experience of pain, may be important in cases of intractable chronic pain to avoid patients' lives becoming dominated by unsuccessful efforts to cope with and control pain (McCracken and Eccleston, 2003; Keefe et al., 2004) and may also be beneficial for physical functioning (Vowles, McNeil, Gross, McDaniel, Mouse, Bates, Gallimore and McCall, 2007). On a more general level, it has been shown that *mindfulness*, i.e. a dispassionate, non-evaluative, receptive and sustained moment-to-moment awareness of and attention to what is taking place in the present, including physical sensations, perceptions, affective states, thoughts, and imagery (Brown and Ryan, 2003; Grossman, Niemann, Schmidt and Walach, 2004) may reduce symptoms and improve the general quality of life of patients with chronic pain (McCracken, Gauntlett-Gilbert and Vowles, 2007).

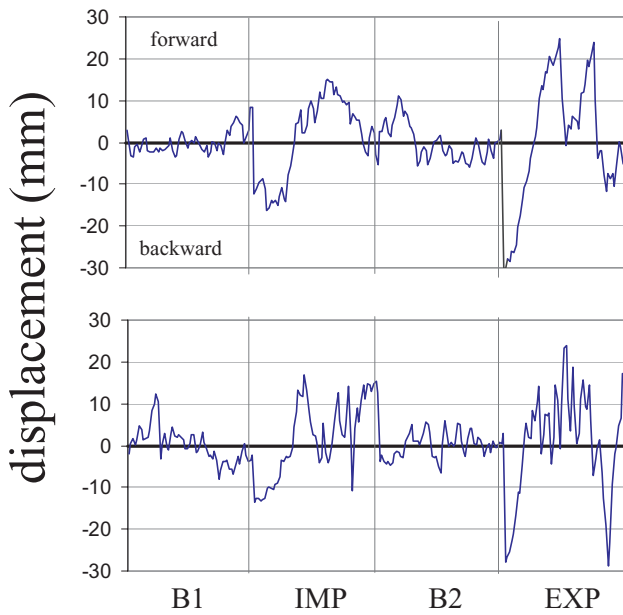
Is being highly hypnotizable – a 'high' – a risk factor for the development of chronic pain?

Subjects highly susceptible to hypnosis (Highs) may exhibit a higher vulnerability to chronic pain (Wickramasekera, Pope and Kolm, 1996; Crawford, Knebel, Kaplan,

Vendemia, Xie, Jamieson and Pribram, 1998) as well as to phobias (Frankel and Orne, 1976; John, Hollander and Perry, 1983; Crawford and Barabasz, 1993) and to post-traumatic stress disorder (PTSD; Stutman and Bliss, 1985; Spiegel, Hunt and Dondershine, 1988; Bryant et al., 2001). In addition, women with a medium hypnotizability have been shown to complain of various physical symptoms more often than those with low hypnotizability (Lows; Younger, Rossetti, Borkardt, Smith, Tasso and Nash, 2007). The high risk model of threat perception (Wickramasekera, 1979; 1988; 1993; Wickramasekera, Pope and Kolm, 1996), based on electrodermal activity studies, states that the development of chronic pain as well as reinforcement of phobia/PTSD occur more frequently in Highs because of their tendency to amplify somatic symptoms and to transduce threat perception into somatic/autonomic symptoms. As a matter of fact, the possibility of the general population to re-experience pain as a real perception, out of hypnosis, is supported by the observation that both memory (Albanese, Duerden, Rainville and Duncan, 2007) and imagery of pain (Raij, Numminen, Narvanen, Hiltunen and Hari, 2005) are associated with cerebral activations roughly similar to those induced by physically evoked pain, as occurs for various sensory modalities (see Carli, Cavallaro, Rendo and Santarcangelo, 2007). However, only the hypnotic suggestion of pain seems to elicit the same activations as physically induced pain (Derbyshire, Whalley, Stenger and Oakley, 2004), which is consistent with the hypothesis of a greater vulnerability of Highs to the development of chronic pain.

Indeed, it is widely accepted that Highs can experience imagery as true perception not only subjectively, but also from behavioural and physiological points of view. For instance, effective instructions of analgesia elicit congruent changes in the activity of the pain neuromatrix (Crawford et al., 1998; Danziger, Fournier, Bouhassira, Michaud, De Broucker, Santarcangelo, Carli, Chertock and Willer, 1998; Croft, Williams, Haenschel and Gruzelier, 2002; De Pascalis, Cacace and Massicotte, 2004; Faymonville, Boly and Laureys, 2006) as well as in the modulation of the spinal nociceptive response (Kiernan, Dane, Phillips and Price, 1995; Danziger et al., 1998; Sandrini, Milanov, Malaguti, Nigrelli, Moglia and Nappi, 2000) and in the vascular correlates of acute pain (Jambrik, Carli, Rudish, Varga, Forster and Santarcangelo, 2005b). It is even more impressive, however, that suggestions not describing any expected behaviour and/or sensory stimulation associated with a specific guided imagery (implicit suggestion) elicit the same behaviour induced by an explicit suggestion (see Figure 1), in subjects not reporting any knowledge and expectation about the behavioural responses appropriate to the situational demand (Carli, Rendo, Sebastiani and Santarcangelo, 2006).

Moreover, the role of the autonomic state of the organism in the subjective experience (considered by Wickramasekera one of the factors contributing to the development of chronic pain) has been demonstrated by studies showing that cardiovascular activity is monitored in cerebral areas – insula, cingulate, medial and inferior frontal gyrus, somato-motor cortex, thalamus – connected with structures of the medial prefrontal brain, providing a cortical association system for higher control of autonomic functions and contributing to a visceral awareness which then becomes a part of the subjective experience (see Pollatos, Schandry, Auer and Kaufmann, 2007). Thus, in the general population an autonomic involvement in the development of chronic pain might be expected. Yet our experimental findings on cardiovascular responses (Santarcangelo and Sebastiani, 2004; Jambrik, Venneri, Varga, Rigo, Borges and Picano, 2004a; Jambrik, Sebastiani, Picano, Ghelarducci and Santarcangelo, 2005a; Jambrik et al., 2005b; Santarcangelo, Varanini, Carli, Migliorini, Fontani and Balocchi, 2006) suggest that Highs can ‘buffer’ or suppress the cardiovascular correlates of stress (Santarcangelo and Sebastiani, 2004;



(modified from Carli et al, *IJCEH* 2006)

Figure 1. Body displacement in the sagittal plane (evaluated at the level of the second thoracic vertebra) in a representative subject.

Note: Not hypnotized subjects stood barefoot, with feet together and eyes closed during the explicit suggestion of falling back (EXP) and during suggestions describing that the carpet under their feet was being pulled forward (IMP, implicit suggestion of falling back). Subjects exhibited a similar backward body displacement during EXP and IMP.

Jambrik, Santarcangelo, Ghelarducci, Picano and Sebastiani, 2004b; Jambrik et al., 2005a) and experimental pain (Jambrik et al., 2005b; Santarcangelo et al., 2006); thus, in these subjects, the autonomic contribution to the development of chronic pain would be expected to be lower than in Lows. This might counteract Highs' greater ability to activate the pain neuromatrix while remembering and/or imagining pain. In line with this prediction, preliminary results from our laboratory do not confirm a greater number of highs among fibromyalgia female patients compared with healthy women, although a possible difference among the patients with chronic pain and healthy controls might have been masked by the slight prevalence of Highs found among healthy women compared with males and by the possible peculiar characteristics of fibromyalgic patients (see Figure 2).

Finally, the mean scores reported in our laboratory by 51 women with fibromyalgia and 47 otherwise healthy women on the Tellegen Absorption Scale (TAS) were not significantly different (unpublished observation), which contrasts with the hypothesized role of a high fantasy proneness – peculiar to Highs – in the development of chronic pain (Wickramasekera et al., 1996; Crawford et al., 1998).

Is being highly hypnotizable relevant for chronic pain treatment?

A number of reviews of controlled studies on the effectiveness of hypnosis in the control of pain have been published (Patterson and Jensen, 2003; Milling, Kirsch, Allen and

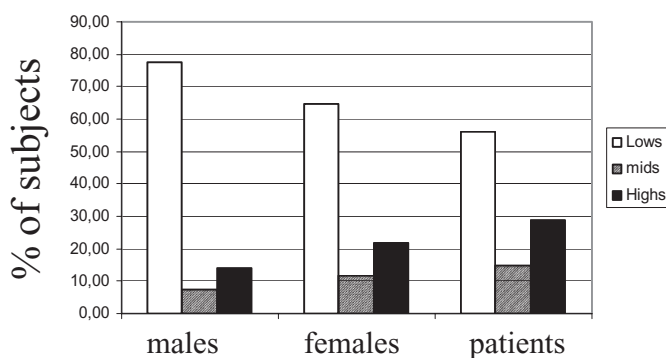


Figure 2. Percentage of low (Lows, score < 3, white columns), medium (Mids, score 4–7, grey columns) and highly hypnotizable (Highs, score > 8, black columns) subjects among healthy males (N = 320), healthy females (N = 449) and fibromyalgic females (N = 59) according to the Stanford Hypnotic Susceptibility Scale, form C.

Note: The patients (medium educational level), all females, belonged to a group of 270 females coming from all Italian regions. They had joined a research programme held at the Department of Physiology of the University of Siena and aimed at defining the psychophysical and psychological characteristics of chronic pain. Controls were students at the University of Siena and Pisa. Patients (age: 25–72) and controls (age: 18–28) were not age-matched.

Reutenauer, 2005; Jensen and Patterson, 2006; Milling, Reardon and Carosella, 2006). Hypnotic treatment reduces pain perception when used alone and contributes significantly to analgesia when used in combination with other treatments (Jensen and Patterson, 2006). It has longer lasting effects than medication management, physical therapy, education, biofeedback, autogenic and other relaxation training. Yet, the specific role of each component of the hypnotic treatment in hypnotic analgesia – suggestibility, hypnotizability, relaxation, expectancy, perceived control over pain – is not fully understood.

The observation of a similar effective hypnotic analgesia in subjects with high and medium levels of hypnotic suggestibility (Montgomery, Du Hamel and Redd, 2000) and, sometimes, even in Lows (Jensen, Hanley, Engel, Romano, Barber, Cardenas, Craft, Hoffman and Patterson, 2005), makes this topic particularly intriguing and suggests the possibility that chronic pain represents a distinct ‘state’ modifying the interaction among the components of hypnotic responding (Benham, Woody, Wilson and Nash, 2006) and, maybe, inducing analgesia through different mechanisms in patients with various level of hypnotizability. For instance, relaxation does not seem to account for the reduction of pain in Highs (Castel, Perez, Sala, Padrol and Rull, 2007; Appel and Bleiberg, 2005), while the role of expectation has not been definitely assessed because some findings indicate it to be a mediator of the effectiveness of hypnotic treatments (Milling et al., 2006; Milling, Shores, Coursen, Menario and Farris, 2007) and others discount its contribution (Castel et al., 2006). Suggestibility could be enhanced by situational variables, i.e. due to the presence of chronic pain and expectancies for pain relief (Milling et al., 2005), which might account also for the paradoxical experience of analgesia reported by patients with low hypnotizability. Indeed, the relationship between hypnotizability and effectiveness of hypnotic analgesia in patients is weaker than in healthy subjects undergoing nociceptive stimulation (Patterson and Jensen, 2003), as shown also in a group of low hypnotizable fibromyalgic patients from our laboratory. At variance with Highs, experiencing pain reduction during the specific suggestion of analgesia, they exhibited a progressive pain reduction throughout the experimental session and even after its end.

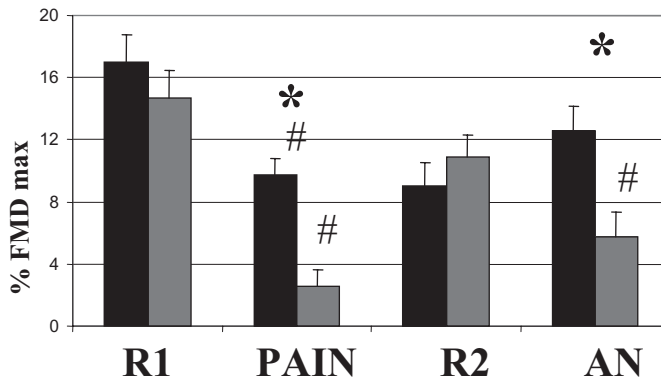
In these patients, relaxation was not responsible for analgesia because a similar pain reduction was reported when mental stress, instead of instructions of relaxation, was administered immediately before the suggestions of analgesia in sessions not including any hypnotic induction. On the other hand, since age-matched, healthy, low hypnotizable subjects undergoing painful stimulation during relaxation and suggestions of analgesia did not experience decreased pain, it might be suggested that chronic pain itself modifies the patients' response to hypnotic treatment leading to changes in the pain coping strategies and, maybe, enhancing the patients' ability of a placebo response (Carli, Suman, Capano and Santarcangelo, 2004; Carli, Suman, Biasi, Marcolongo and Santarcangelo, in press). This is consistent with the observation that placebo analgesia is more effective in patients than in healthy subjects undergoing painful stimulation (Charron, Rainville and Marchand, 2006) due to a modulation of the affective component of pain occurring in the former. However, although hypnotic and placebo analgesia (and, thus, reasonably, analgesia in Highs and Lows) share common cortical activation patterns (Kupers, Faymonville and Laureys, 2005), the two processes might represent the result of different cognitive strategies.

Is being highly hypnotizable desirable?

A natural protection of Highs against the cardiovascular effects of acute pain and stress has been recently suggested on the basis of studies of endothelial function (Santarcangelo and Sebastiani, 2004; Jambrik et al., 2004b, 2005a, b). This contrasts with earlier studies on electrodermal activity suggesting a sympathetic hyper-reactivity in Highs (Wickramasekera, 1979, 1988, 1993; Wickramasekera, Pope and Kolm, 1996), which would potentially make them more vulnerable to cardiovascular disease. In our view, the discrepancy in findings is due to the complex, cognitive/affective modulation of electrodermal activity whose changes cannot be easily interpreted.

Endothelial function is an expression of the response of vascular endothelium to the shear stress due to blood flow. When flow increases, as occurs soon after occlusion of the vessel, endothelial cells elicit a vasodilation mainly through the production of nitric oxide. This flow-mediated vasodilation (FMD) has an emerging role as a diagnostic tool and as a prognostic factor of cardiac risk. It is transiently reduced by acute mental stress likely to be due to an acute accumulation of catecholamines and endothelium-derived endothelin-1 (see Jambrik et al., 2004a, 2004b; 2005). In line with results obtained during mental stress (Jambrik et al., 2004b; 2005a), during acute experimental pain (see Figure 3) the reduction of FMD in Highs is significantly smaller than in Lows and a complete FMD recovery occurs during suggestions of analgesia (Jambrik et al., 2005b).

The mechanisms responsible for the differences in FMD between healthy Highs and lows undergoing stress and experimental pain, presently under investigation, might consist of: a) a different expression and/or functional characteristics of the substances produced by endothelial cells following shear stress, i.e., endothelin and NO, and; b) different after occlusion blood flow due to different changes in the sympathetically-controlled vascular resistance. The first hypothesis prompted genetics/molecular investigations and its occurrence would greatly reduce the possibility of preventing the vascular damage associated with chronic pain through psychological interventions; in contrast, the second hypothesis would represent the basis of a promising approach to the prevention of the vascular effects of stress and acute pain. It would be along the same lines as earlier findings (Hoffmann, Benson, Arns, Stainbrook, Young and Gill, 1982), showing that when healthy subjects trained or not trained in autogenic training performed physical



(modified from Jambrik et al., Pain, 2005)

Figure 3. Endothelial function (FMD max) during rest (R1, R2) and stimulation conditions (PAIN, AN).

Note: Highs (black bars) and Lows (white bars) mean values and standard errors are represented. In both groups a significant FMD reduction was observed during PAIN, but in Highs the reduction was significantly lower than in Lows and recovered completely during AN (#, between stimulation and basal conditions; *, between Groups significant difference).

exercise, the blood catecholamine levels were similar in both groups, but the hemodynamic response was present only in non-trained participants. In this respect, being a high, and/or having psychological characteristics inducing the same vascular responses observed in Highs, might be very desirable. In fact, shear stress induces cascade responses leading from short- to long-term cardiovascular damage (Davies, 1995; Resnick, Yahav, Shay-Salit, Shushy, Schubert, Zilberman and Wofovitz, 2003), and it may be conceived that the subjects able to buffer the short-term responses may also be protected against the long-term effects of pain. Results concerning heart rate are less clear, although studies on the possible lower vulnerability of Highs to the cardiovascular effects of stress did begin with the observation of a lack of heart rate increases associated with fear-like stimulation in nonhypnotized Highs (Sebastiani, Simoni, Gemignani, Ghelarducci and Santarcangelo, 2003).

In experiments including painful stimulation and suggestions of analgesia, a different heart rate variability that is the expression of the sympathetic-parasympathetic control of heart rate (see Figure 4) was found in Highs and Lows (Balocchi, Varanini, Menicucci, Santarcangelo, Migliorini, Fontani and Carli, 2005; Santarcangelo et al., 2006) even in the absence of heart rate differences.

Indeed, in basal conditions, the best correlation between consecutive RR distances (that is the distances between consecutive R waves of the ECG) and their standard deviation (SD) was linear in Highs, but not in Lows (see Table 1). This linear correlation was abolished by painful stimulation and was not restored by the suggestion of analgesia. Also the best correlation between indices of sympathetic activation (Figure 4, Table 1) extracted in the time (CSI) and frequency domain (LF/HF) was linear in Highs, but not in Lows; it was abolished by nociceptive stimulation and restored by the suggestions of analgesia. This indicates, in Highs, a complex elaboration of the suggestion of analgesia likely to depend on the intervention of mechanisms inducing a different sympathetic-parasympathetic balance, with respect to basal conditions. In particular, the contribution of the Very Low Frequency component of heart rate variability, related to the endothelial

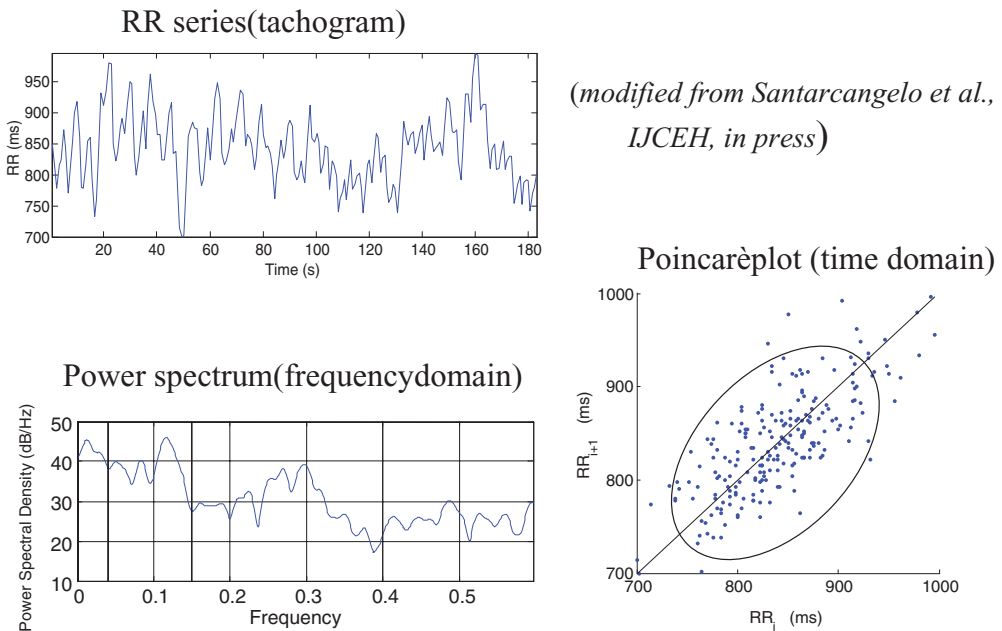


Figure 4. The RR series (tachogram, A) can be analysed in the frequency domain (B) through spectral analysis (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) providing the two major oscillatory components of heart rate variability (HRV), one synchronous with respiration and related to parasympathetic activity (High Frequency, HF, 0.15–0.4 Hz), and the other corresponding to the baroreceptor reflex activity (0.04–0.15 Hz), as well as in the time domain (C), i.e. through the indexes extracted from the Poincaré Plot providing a cloud of points having coordinates (R_i, R_{i+1}) .

Note: The two quantities $sd1$ and $sd2$ are different expressions of the variability of the RR series: $sd2$ contains the overall (sympathetic and parasympathetic) variability, while $sd1$ retains only the parasympathetic one. The $sd2/sd1$ ratio (CSI, cardiac sympathetic index) is a time-domain measure of the sympathetic-parasympathetic balance and is analogous, but not identical, to the frequency-domain index LF/HF (Balocchi, Cantini, Varanini, Raimondi, Legramante and Macerata, 2006). Indeed, while HF and $sd1$ are measures of the parasympathetic variability, LF is a measure of the sympathetic variability not including (at variance with $sd2$) the frequency components of heart rate variability below 0.04 Hz (Very Low Frequency, VLF).

and renin-angiotensin control of the vessels diameter, might be different in the two groups and account for different correlations between CSI and LF/HF in various experimental conditions. Studies in progress are aimed at identifying the mechanisms responsible for this different sympathetic-parasympathetic control in the two groups, their functional relevance and possible prognostic role.

Conclusions

On the basis of our experimental results, being a high does not represent a clear risk for the development of chronic pain and may be a favourable prognostic factor against the possible cardiovascular consequences of chronic pain. In addition, due to the possibility of modulating the Highs' immune system activity (Gruzelier, 2002; Naito, Laidlaw, Henderson, Farahani, Dwivedi and Gruzelier, 2003), the immune deficiency associated with chronic pain (Machelska et al., 2001; Niv and Devor, 2004) might be less serious and/or more easily treated in highs.

Table 1. Best correlations between indexes of heart rate variability extracted in the time and frequency domain

condition	correlation		Highs (N = 10)		Lows (N = 8)
B1	RR-SD	linear	R = 0.777**	inverse	R = 0.550*
	LF/HF-CSI	linear	R = 0.718*		
PAIN	RR-SD			inverse	R = 0.531*
	LF/HF-CSI				
B2	RR-SD	linear	R = 0.675*	quadratic	R = 0.939***
	LF/HF-CSI	linear	R = 0.897***		
AN	RR-SD			inverse	R = 0.547*
	LF/HF-CSI	linear	R = 0.770**		
B3	RR-SD	linear	R = 0.702*		
	LF/HF-CSI	linear	R = 0.705**		

1, B2, B3: resting conditions; PAIN, painful stimulation; AN, painful stimulation and suggestions of analgesia.

RR, time interval between consecutive R waves of ECG; SD, standard deviation; LF/HF and CSI, sympathetic.

activation indexes extracted in the frequency and time domain, respectively.

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

Notwithstanding, being a high does not seem to be particularly relevant in the relief of chronic pain. Going beyond a possible improvement of the placebo response due to a stronger expectancy and desire for pain relief in chronic pain patients compared to healthy subjects (Vase, Robinson, Verne and Price, 2003), it is also likely that patients with chronic pain have developed individual coping strategies to manage living with their illness, and they may apply these techniques when faced with suggestions for analgesia. For example, they may use relaxation, attention/distraction (Bushnell, Villemure and Duncan, 2004) or enter into a state of mindfulness. More research is needed to clarify the correlations between various psychological factors, including hypnotic susceptibility, and their interplay in producing analgesic effects in patients with chronic pain. Finally, it cannot be excluded that psychological characteristics such as mindfulness, well-being, and pain catastrophizing, might be different in Highs and Lows and represent the real agents of the differences between the two groups in pain experience, the development of chronic pain and possible vascular consequences. This might make predictions based only on hypnotizability unreliable.

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