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Masterclass

Enhance placebo, avoid nocebo: How contextual factors affect physiotherapy outcomes

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ABSTRACT

Introduction: Placebo and nocebo represent complex and distinct psychoneurobiological phenomena in which behavioural and neurophysiological modifications occur together with the application of a treatment. Despite a better understanding of this topic in the medical field, little is known about their role in physiotherapy.
Purpose: The aim of this review is: a) to elucidate the neurobiology behind placebo and nocebo effects, b) to describe the role of the contextual factors as modulators of the clinical outcomes in rehabilitation and c) to provide clinical and research guidelines on their uses.
Implications: The physiotherapist's features, the patient's features, the patient–physiotherapist relationship, the characteristics of the treatment and the overall healthcare setting are all contextual factors influencing clinical outcomes. Since every physiotherapy treatment determines a specific and a contextual effect, physiotherapists should manage the contextual factors as a boosting element of any manual therapy to improve placebo effects and avoid detrimental nocebo effects.

1. Introduction

Every day physiotherapists (PTs) use different tools, such as manual techniques and exercises, to achieve their main professional goals: the improvement of pain, disability and patient's self-perceived health condition. The management of placebo and avoidance of nocebo responses have recently been suggested as promising additional clinical strategies (Gay and Bishop, 2014), generating a wide debate in manual therapy research (Benz and Flynn, 2013; Ingram et al., 2013; Kamper and Williams, 2013).

Placebo and nocebo represent complex and distinct psychoneurobiological phenomena in which behavioural and neurophysiological modifications occur following application of a treatment. The placebo (Latin "I shall please") is created by the positive psychosocial context that is capable of influencing the patient's brain (Benedetti, 2013). Instead, the nocebo (Latin "I shall harm") is the result of the negative ritual and therapeutic act on the patient's mind and body (Benedetti et al., 2007; Colloca and Benedetti, 2007; Colloca and Miller, 2011c).

From a psychobiological perspective (Fig. 1), conscious expectation and the unconscious classical conditioning, reward-learning, observational and social learning, modulation of anxiety, desire, motivation, memory and prior experience, somatic focus, personality traits and genetics work as facilitators of placebo or nocebo (Benedetti et al., 2011; Colloca and Miller, 2011b; Colloca, 2014) and modulate different responses across several diseases, illnesses, and treatment methods (Benedetti, 2008; Enck et al., 2013; Schedlowski et al., 2015). Although some attempts to identify (Michener et al., 2013) and to measure (Michener et al., 2015) the placebo response induced by sham techniques have been reported, to date the role of placebo response seems to be poorly recognized and applied by PTs in the clinical setting (Bialosky et al., 2011) and nocebo is still scarcely considered as a possible variable negatively influencing rehabilitation outcome. Agreeing that the conscious reinforcement of placebo strategies could represent an additional opportunity for every PT to improve their clinical outcomes, this masterclass aims to:

a) Synthesize the neurobiological mechanisms underlying the placebo and nocebo responses;
b) Describe the contextual factors as modulators of clinical outcomes in musculoskeletal rehabilitation;

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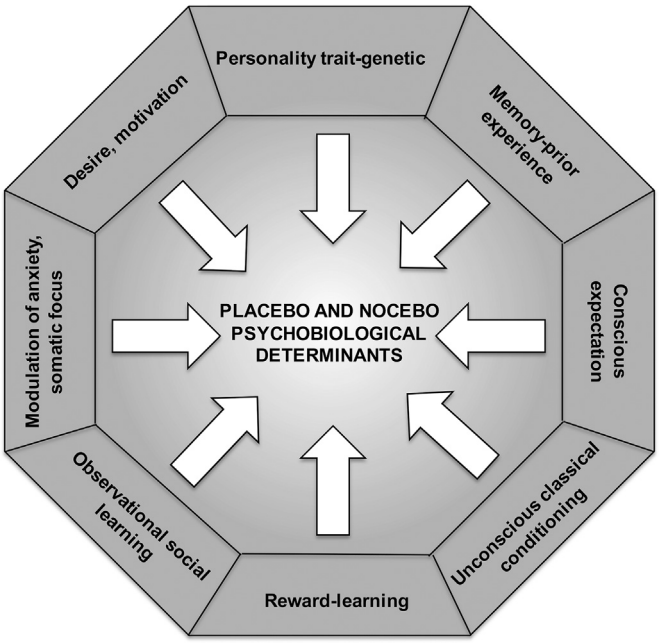

Fig. 1. Placebo and nocebo psychobiological determinants.

c) Provide guidance for the clinical implementation of placebo enhancement and/or nocebo avoidance;
d) Identify possible new lines of investigation in manual therapy research.

2. The neurobiological mechanisms behind placebo and nocebo responses

Pain and motor performance are the most frequently used models to describe the neural network involved during the placebo and nocebo responses (Tracey, 2010; Carlino et al., 2011; Colloca et al., 2013; Colagiuri et al., 2015).

2.1. Pain

Placebo and nocebo engage distinct top-down modulatory systems using different key neurotransmitters. Endogenous opioids, dopamine, cannabinoids, oxytocin and vasopressin are involved in placebo while cholecystokinin, dopamine, opioid deactivation and cyclooxygenase-prostaglandins activation interact with nocebo (Finniss and Benedetti, 2005; Benedetti and Amanzio, 2013; Carlino and Benedetti, 2016). Placebo analgesia and nocebo hyperalgesia largely involve, with opposite activation, numerous brain areas (Table 1).

Among them, placebo analgesia is mostly associated with an increased functional coupling of the dorsolateral prefrontal cortex, the anterior cingulate cortex, the hypothalamus, the amygdala, the periaqueductal grey and decreased activity in pain processing areas such as the thalamus, insula and the somatosensory cortex (Benedetti et al., 2005; Benedetti et al., 2011; Amanzio et al., 2013; Benedetti, 2014). On the contrary, negative expectations of pain increase the activation of affective-cognitive pain regions like the anterior cingulate cortex, the prefrontal cortex, the insula and the hippocampus. Furthermore, placebo and nocebo are capable of modulating pain processing at the spinal level (Benedetti et al., 2007; Colloca and Benedetti, 2007; Schedlowski et al., 2015). For a graphical representation see Fig. 2A and B.

2.2. Motor performance

Placebo and nocebo influence the activity of the motor system and the consequent motor performance (Beedie and Foad, 2009; Beedie, 2010; Pollo et al., 2011; Carlino et al., 2014b). It has been shown that placebo induces an increase of dopamine in the striatum and a change of neural activity in the basal ganglia and in limbic areas of the brain in patients affected by Parkinson disease (Frisaldi et al., 2014; Benedetti et al., 2016). Enhanced corticospinal system excitability (Fiorio et al., 2014) and reduced fatigue by modulating readiness potential during the anticipatory phase of movement (Piedimonte et al., 2015) were displayed in healthy subjects. Similarly, a nocebo procedure in which the induced expectation decreases force production modulated the corticospinal circuits influencing motor performance (Emadi Andani et al., 2015).

3. The contextual factors optimize the rehabilitation outcomes

The psychosocial context and the therapeutic ritual around the patient can also influence the patient's brain activity and the therapeutic outcome such as satisfaction and perceived effect (Colloca and Benedetti, 2005; Benedetti, 2013; Carlino et al., 2014a). As reported in Fig. 3, the physiotherapist's and patient's features, the patient–physiotherapist relationship, the characteristics of the treatment and the overall healthcare setting are the most relevant categories of contextual factors involved in placebo or nocebo effects (Blasi et al., 2001).

3.1. Physiotherapist's features

A “physiotherapist's effect” is present and influences the outcome of treatment in patients with musculoskeletal disorders (Lewis et al., 2010).

3.1.1. Professional reputation and appearance

The perception of expertise, professionalism, qualification, reputation and the level of training of PTs are important elements for the patient and can contribute to modifying the clinical outcome in musculoskeletal disorders (Hush et al., 2011; Bishop et al., 2013a; O'Keeffe et al., 2015). Moreover the way a therapist dresses is able to influence the patient's perception of care (Petrilli et al., 2015). Recently the results of a study by Mercer et al. (2008) reported that a laboratory coat and tailored clothing were ranked respectively most professional and preferred, by patients with low back pain (LBP). By contrast, patients were less satisfied if the professional appearance was poor and if PTs wore jeans during clinical practice (Mercer et al., 2008; Hush et al., 2011).

3.1.2. Beliefs and behaviours

Enthusiastic practitioners and their optimism or pessimism regarding the nature of a treatment can have an active effect on the outcome (Autret et al., 2012; Witt et al., 2012; Vaughn, 2014). This is a self-fulfilling prophecy whereby the convincement of a practitioner about the patient's outcome leads to an improvement (“Pygmalion effect” – “Rosenthal effect”) or a worsening (“Golem effect”) of the outcome itself (Sternberg et al., 2011). Recent evidence linked the attitudes and beliefs of patients with LBP with the attitudes and beliefs of the health care professional (including PTs) they had consulted (Darlow et al., 2012). Patients appreciated the PT's aptitude to encourage questions and to answer the patient's queries, to explore disease and illness experience and to trust their opinion. The PT's ability to deliver positive feedback, to give clear prognostic information and explanation about the patient's

Table 1
Description of brain areas involved in placebo analgesia and nocebo hyperalgesia.

Placebo analgesia	Nocebo hyperalgesia
Rostral anterior cingulate cortex, Hypothalamus,	Hippocampus,
Amygdala,	Dorsal horn of spinal cord,
Periaqueductal gray,	Nucleus accumbens,
Rostral ventro-medial medulla,	Thalamus,
Lateral orbitofrontal cortex,	Second somatosensory cortex,
Nucleus accumbens,	Posterior insular cortex,
Dorsolateral prefrontal cortex,	Caudal anterior cingulate cortex,
Ventrolateral prefrontal cortex,	Head of the caudate,
Dorsal horn of spinal cord,	Cerebellum,
Thalamus,	Contralateral nucleus cuneiformis,
Anterior insular cortex,	Parietal operculum,
Primary and secondary somatosensory cortex,	Bilateral dorsal anterior cingulate cortex,
Putamen,	Left frontal and parietal operculum,
Caudate nucleus,	Orbitofrontal cortex,
Striatum,	Lateral prefrontal cortex,
Supramarginal gyrus,	
Left inferior parietal lobule.	
The parabrachial nuclei	

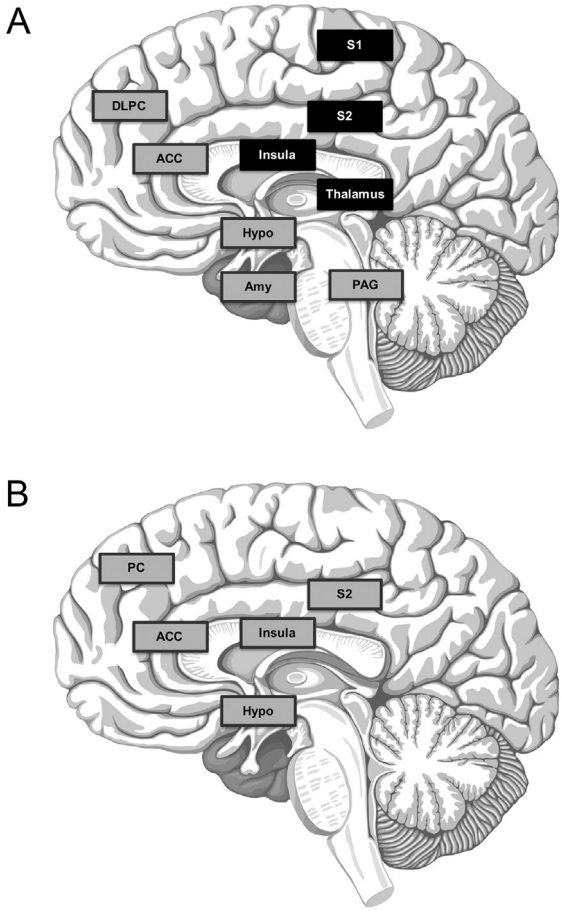

Fig. 2. Brain areas most involved in placebo analgesia (A) and nocebo hyperalgesia (B). For complete listing see Table 1. In grey area activated, in black area deactivated. DLPC: dorsolateral prefrontal cortex, ACC: anterior cingulate cortex; S1: primary somatosensory cortex; Hypo: hypothalamus; Amy: amigdala; PAG: periaqueductal gray; S2: secondary somatosensory cortex; PC: prefrontal cortex.

condition and the treatment can positively interact with the results of therapy (Hall et al., 2010; Hush et al., 2011; Oliveira et al., 2012; Pinto et al., 2012; Pincus et al., 2013; O'Keeffe et al., 2015). In contrast, PTs should avoid showing nervousness, spending too much time reading patient charts, using too many technical words or be uncooperative or in a hurry during the clinical encounter (Oliveira et al., 2012; O'Keeffe et al., 2015).

3.2. Patient's features

The patient's perception and direct experience of care are central elements capable of influencing the placebo analgesia (Vase et al., 2011).

3.2.1. Expectation, preferences and previous experience

The expectation of a treatment can shape the patient's pain experience (Tracey, 2010; Colloca and Miller, 2011d; Atlas and Wager, 2012; Peerdeman et al., 2016). It was recently demonstrated that the general expectations for pain relief strategies had an important influence on pain and disability, in patients with LBP (Bishop et al., 2011) and neck pain (Bishop et al., 2013b). Moreover, expectation is a significant prognostic factor in musculoskeletal pain and is often underestimated by PTs (Barron et al., 2007; Bialosky et al., 2010; Puentedura et al., 2012). The patient's prior experience of care is also a factor that can affect the outcome of the therapy (Colloca and Benedetti, 2006). Indeed, a patient's preferences and previous experiences about a physiotherapy treatment are able to modify the magnitude of the therapeutic response in musculoskeletal rehabilitation just because of the way they are paired with prior positive or negative results (Hush et al., 2011). In contrast, avoiding or ignoring the patient's preferences, expectations and previous experiences can negatively influence the therapeutic outcome (O'Keeffe et al., 2015).

3.2.2. Musculoskeletal condition, gender and age

The phases of the course of the musculoskeletal disorder can influence the outcomes of care such as the satisfaction of the patient (Hills and Kitchen, 2007). Indeed, acute patients reported higher satisfaction with physical therapy care and were more sensitive to a number of PT's features such as expertise, reputation, level of training and professional behaviour than those with chronic conditions who perceived the organization of care as the most significant element (Hush et al., 2011). Moreover, the perception of the quality of physiotherapy care is affected differently in males and females as well as in patients of different age (Stenberg et al., 2012). In particular, the main predictors of satisfaction for male patients were the therapist and treatment outcome, whereas for female patients the most important elements were organization and the communication component of care.

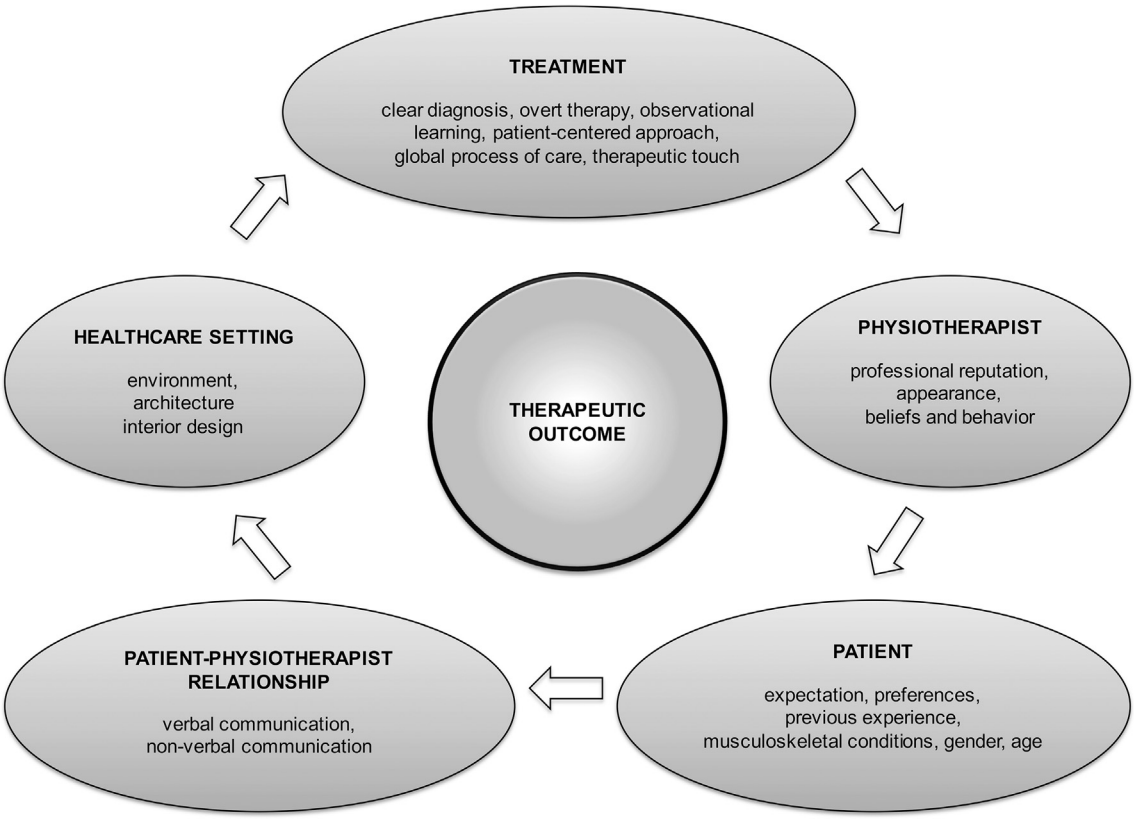

Fig. 3. The contextual factors as modulators of therapeutic outcome.

Older patients seem to be more sensitive to particular aspects of physical therapy care such as access to services and the effectiveness of communication (Hush et al., 2011).

3.3. The patient–physiotherapist relationship

A good patient-PT relationship positively influences outcomes like pain, disability, satisfaction and strengths of the therapeutic alliance (Hall et al., 2010; Ferreira et al., 2013). The clinical encounter is modulated by different factors such as verbal and non-verbal skills (Henry et al., 2012).

3.3.1. Verbal communication

An appropriate verbal communication is a prerequisite of a good therapeutic relationship (Parsons et al., 2007). PTs spend, on talking with the patient, approximately twice the time they pass treating hands-on (Roberts and Bucksey, 2007; Roberts et al., 2013). Active listening and verbal expressions of support and encouragement, humour and sympathy, empathetic and communicative discussion, partnership statements, paraphrasing and requests for the patient's opinion and the language reciprocity correlated with patients' satisfaction and can significantly influence the outcome of the treatment (Hush et al., 2011; Oliveira et al., 2012; Pinto et al., 2012; O'Keeffe et al., 2015). PTs should avoid negative communication, verbal expressions of anxiety, closed questions to gather information and use of social niceties (Oliveira et al., 2012). Patients were dissatisfied when they were interrupted and could not tell their story and when the PT lacked empathy, friendliness, was too confident or behaved arrogantly (O'Keeffe et al., 2015). Furthermore, the use of positive messages associated with treatment for pain relief (e.g. “this treatment is a powerful pain killer”) produces a large placebo analgesia effect in medicine (Vase et al., 2002, 2009). In manual therapy, conversely, associating hands on techniques with positive verbal instructions changed positive expectation and patients' satisfaction, without affecting pain or disability (Bialosky et al., 2014; Riley et al., 2015a, 2015b). Moreover, the use of negative information during the leg flexion test (e.g. “this procedure could lead to a slight increase in pain”) determined an aggravation of pain and poor performance during the test in patients with chronic LBP (Pfingsten et al., 2001).

3.3.2. Non-verbal communication

Facial expression and eye contact represent important elements in therapeutic interaction (Pinto et al., 2012) from which patients deduce meaning (Benedetti, 2013). The facial expression is capable of influencing pain processing (Wieser et al., 2014) and enhancing the placebo analgesia (Valentini et al., 2014). In a clinical context, PTs use non-verbal behaviour such as eye contact, smiling (Roberts and Bucksey, 2007), caring expressions of support and interest, potentially contributing to affecting therapy outcome (Oliveira et al., 2012). Gestures, postures and physical contact along with speech also form an integrated message full of meaning during clinical interactions (Josephson et al., 2015; O'Keeffe et al., 2015). By observing these elements, a patient can infer the therapist's intention and adapt his own behaviour unconsciously with modification of neurohormonal substrate of the oxytocin system (Hostetter, 2011; Feldman, 2012; Benedetti, 2013). PTs regularly use affirmative head nodding, touch, forward leaning and body orientation to facilitate and involve patients to improve satisfaction with the consultation (Roberts and Bucksey, 2007; Oliveira et al., 2012). Additionally, the therapist's ability to interpret the patients' nonverbal body language expressions is an important element of satisfaction during the clinical encounter (Oliveira et al., 2012). Thus, PTs should avoid an inquisitive eye contact, a slanting

position (45° or 90° towards the patient), asymmetrical arm postures, crossed legs, backward leaning and neck relaxation (Oliveira et al., 2012; Pinto et al., 2012).

3.4. Treatment features

Different variables of a treatment can influence the outcome perceived by the patient (Horin et al., 2014).

3.4.1. Clear diagnosis, overt therapy and observational learning

The formulation of a diagnosis, which explains to the patient his disturbances and gives meaning to the patient's illness, is a form of treatment per se (Hopayian and Notley, 2014). Delivering a detailed diagnosis and explanation of the musculoskeletal disorder is appreciated by patients and can influence their satisfaction about the care during the first visit (Hush et al., 2011; Ludvigsson and Enthoven, 2012; Pinto et al., 2012). Moreover, showing and telling patients that a treatment is being applied is important for the creation of the placebo response and modulation of the therapeutic outcome (Colloca et al., 2004). In a postoperative analgesia study, covert administration of analgesic resulted in a slower onset of pain relief than when patients knew when morphine was administered, implying that the initial rapid relief is largely effected through a placebo response (Amanzio et al., 2001). In addition in physiotherapy, the administration of an overt treatment by a mirror feedback was proposed as an effective strategy in chronic LBP (Daffada et al., 2015). Indeed, patients that looked at their back when moving during exercises reported less increase in pain and a faster resolution of their dysfunction (Wand et al., 2012; Diers et al., 2013). Finally, endorsing the positive effects of a therapy in a therapeutic context in which patients could talk to other patients who successfully received the same treatment, or if they watched videos of other patients, can influence placebo analgesia and avoid nocebo (Colloca, 2014). In musculoskeletal rehabilitation, the use of active observation of others' movement improved pain and disability of patients after total knee replacement (Bellelli et al., 2010; Park et al., 2014).

3.4.2. Patient-centred approach and global process of care

Personalizing treatment, taking the patient's opinions into account and use of a patient-centred care seem to influence the results of the treatment (Hush et al., 2011; Oliveira et al., 2012; Pinto et al., 2012; Schoeb and Burge, 2012; O'Keeffe et al., 2015). Moreover, organisational and procedural aspects of physiotherapy such as therapy delivered by the same PT, cleanliness, adequate length of the consultation, punctuality, flexibility with patient appointments, timely and efficient treatment, adequate frequency, duration and follow-up of therapy affect the patient's satisfaction and therapeutic outcome (Hush et al., 2011; Oliveira et al., 2012; O'Keeffe et al., 2015). However, the use of a therapist-centred or biomedical approach, a lack of privacy, an expensive treatment, a too long waiting list, a reduction of patient-PT time, being treated by different PTs or a hastened treatment negatively influences the outcome of therapy (Hush et al., 2011; Oliveira et al., 2012; O'Keeffe et al., 2015).

3.4.3. Therapeutic touch

In a clinical context, PTs apply different forms of touch such as assistive touch, touch used to prepare the patient, touch to provide information, caring touch, touch to provide a therapeutic intervention, and touch used to perceive information (Roger et al., 2002; Bjorbaekmo and Mengshoel, 2016). Touch is a fundamental element of interpersonal interaction (Gallace and Spence, 2010) that regulates the social bonding in humans. This kind of touch information is conducted by a class of cutaneous unmyelinated, low threshold mechanosensitive nerves, called c-tactile afferents that process affiliative tactile stimuli (Zimmerman et al., 2014; Ellingsen et al., 2016). Moreover touch in the therapeutic setting acts as a useful strategy to relieve musculoskeletal pain (So et al., 2008; Monroe, 2009). When moderate and light pressure massage was compared, only moderate pressure contributed to enhance pain, depression and anxiety (Field, 2014). Furthermore, moderate pressure massage was capable of modifying neurophysiological parameters such as heart rate, improved vagal activity, decreased cortisol levels, enhanced serotonin and dopamine levels and influences cortical and spinal excitability and inhibits nociceptive responses at a subcortical and cortical level (Field et al., 2005, 2010; Sefton et al., 2011; Field, 2014; Mancini et al., 2015).

3.5. Healthcare setting features

The healing environment and the use of combined positive distractors in a therapeutic context can influence the patient's outcomes such as pain, stress and anxiety (Ulrich et al., 2010).

3.5.1. Environment

Different sensory elements of the environment can modulate the patient's outcome. Environments with natural lighting, monitored low noise levels, with relaxing and soft music are more desirable (Schweitzer et al., 2004; Brown and Gallant, 2006; Dijkstra et al., 2006; Malenbaum et al., 2008; Ulrich et al., 2008; Cesario, 2009; Drahota et al., 2012; Laursen et al., 2014). Moreover, the use of pleasing aromas and an adequate temperature are important factors to be considered in a therapeutic context (Schweitzer et al., 2004; Dijkstra et al., 2006).

3.5.2. Architecture

Structural aspects of the healthcare environment can influence the patient's perception of care and pain perception (de Tommaso et al., 2013). Environments that integrate windows and skylights in the workplace and comfortable and private therapeutic settings are more appreciated by patients (Schweitzer et al., 2004; Brown and Gallant, 2006; Dijkstra et al., 2006; Ulrich et al., 2008; Cesario, 2009). Furthermore, it is advisable to use supportive indicators such as highly visible and easy to read signs, parking information, accessible entrances, clear and consistent verbal or written directions, information desks and accessible electronic information (Cesario, 2009). Indeed, good access to services, particularly convenient clinic hours, location, parking, and available and approachable support staff are perceived as important elements for the patient (Hush et al., 2011).

3.5.3. Interior design

Decorations and ornaments can impact on the health status of the patient. Nature artworks that include green vegetation, flowers, water and a setting with a view of nature that integrates plants or garden ornaments have a calming effect (Schweitzer et al., 2004; Brown and Gallant, 2006; Dijkstra et al., 2006; Malenbaum et al., 2008; Ulrich et al., 2008; Cesario, 2009; Laursen et al., 2014). Colour schemes based on soothing shades also seem to modulate the patient's experience of care (Brown and Gallant, 2006). However, the meaning of colour differs among individuals and should be culturally suitable for the patient population it is intended to serve (Schweitzer et al., 2004; Cesario, 2009).

4. Implications for clinicians: maximise placebo, minimize nocebo

In therapeutic settings, placebo and nocebo effects are commonly detected. Various systematic reviews have observed

placebo when continuous subjective measures of disease are adopted, but not when binary subjective or objective measures are applied (Hróbjartsson and Gøtzsche, 2001, 2004, 2010). This advocates that placebo does not influence the disease but affects the illness as subjective perceptions of the patient experience (Miller and Colloca, 2009; Miller et al., 2009). Indeed placebo and nocebo can positively and negatively impact on impairments and disabilities such as pain (Vase et al., 2002; Vase et al., 2009; Petersen et al., 2014), motor performance (Beedie and Foad, 2009; Beedie, 2010; Pollo et al., 2011; Carlino et al., 2014b) and satisfaction with musculoskeletal therapy (Hush et al., 2011). Therefore, PTs should consider it in clinical practice and be aware of maximizing placebo and eliminating nocebo (Enck et al., 2013; Klinger et al., 2014). Table 2 provides guidelines on the application of placebo.

From a clinical point of view, placebo and nocebo elements are always present during a therapeutic intervention. Every healthcare intervention is formed by two factors: a specific/active biological component and a contextual/psycho-social one (Benedetti, 2013). These contextual elements interact with the specific effect of the therapy by either increasing or decreasing the global effect of treatment (Colloca and Benedetti, 2005; Carlino et al., 2014a). Manual therapy also presents a specific biomechanical and neurophysiological mechanism that could be modulated by the context (Bialosky et al., 2009; Bialosky et al., 2011; Miciak et al., 2012; Bishop et al., 2015b). For PTs it is essential to transfer this knowledge in clinical practice to improve therapy application and outcome (Gay and Bishop, 2014; Bishop et al., 2015a). Fig. 4 shows the relevance of adding different contextual factors with the specific effect of a treatment.

PTs should remember that patient satisfaction is determined more by interactions with the PT and the process of care rather than the outcome of treatment (Hush et al., 2011). Therefore, it is useful to strengthen the therapeutic relationship, the healing rituals and treatment setting during the clinical encounter (Barrett et al., 2006; Miller and Kaptchuk, 2008; Kaptchuk, 2011). In the therapeutic arena multiple signs and cues convey a hidden meaning that is

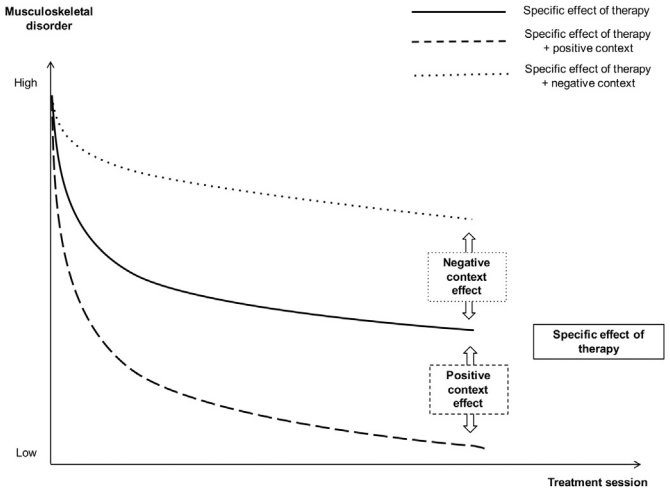

Fig. 4. The modulation of the specific effect of therapy by positive and negative context.

essential for the perception and interpretation of care and that may be just as important as the specific effect of the treatment (Benedetti, 2002; Miller and Colloca, 2010; Benedetti and Amanzio, 2011; Benedetti, 2012).

Beside placebo and nocebo, other conditions such as the natural history of the disease, the regression to the mean, biases by clinicians and patients, unidentified co-interventions or adverse side effects in the placebo group in a randomized controlled clinical trial (RCT) can modify the outcomes of therapy and can disguise recovery or exacerbation (Benedetti, 2008; Colloca and Miller, 2011c). Fig. 5 provides a graphical synopsis about the different elements that can influence the global therapeutic outcome.

Whilst placebo is a real and powerful phenomenon with a supportive evidence of action, it must be clear that the placebo

Table 2
Strategies to enhance placebo in physiotherapy.

Key points
Physiotherapist's and patient's features
• Improve professionalism, reputation, training and expertise;
• Use a laboratory coat or tailored clothing;
• Be optimistic during the consultation and regarding the dysfunction;
• Deliver clear diagnosis, prognosis and explanation of the patient's problem;
• Explore the patient's disease and illness, request and trust the patient's opinion;
• Encourage questions, answer queries from the patient, deliver positive feedback;
• Investigate expectation, preferences and the patient's previous experiences;
• Consider the phase of the musculoskeletal condition, gender and age of the patient;
Patient-physiotherapist relationship
• Be warm, confident, friendly, relaxed and open during the clinical encounter
• Use verbal expressions of empathy, support, sympathy and language reciprocity;
• Adopt psychosocial talk, partnership statements and paraphrase;
• Use positive messages associated with treatment for pain relief;
• Use eye contact, smiling, caring expressions of support and interest;
• Use affirmative head nodding, forward leaning and open body posture;
• Interpret patient's nonverbal body language expressions;
Treatment features
• Use open treatment, show and tell the patient that a therapy is applied;
• Boost the patient's willingness to talk to other patients who undergo the same treatment with positive results;
• Use patient-centred care, personalize the treatment;
• Deliver the treatment by the same physiotherapist in a clean and private environment,
• Set appointments with adequate length, punctuality, frequency, follow-up;
• Use touch to assist, prepare, inform, care of, perceive and treat patients;
Healthcare setting features
• Combine positive distractors as light, music, temperature and aromas,
• Adopt supportive indications to facilitate access to physiotherapy service;
• Decorate the therapeutic environment with artworks and ornaments;

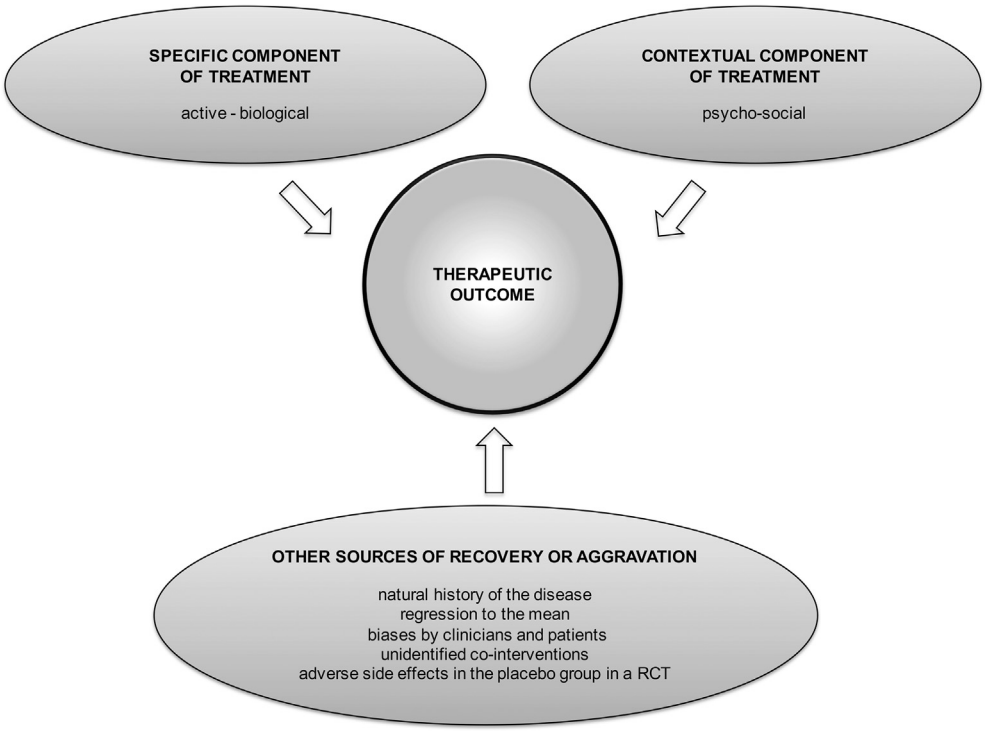

Fig. 5. Different determinant of global therapeutic outcome.

intervention should not be based on unethical principles or deception and should not be a substitute for other more effective treatments (Miller and Colloca, 2009). It is ethical to use it as a boosting strategy combined with the best available therapy to improve clinical outcomes of patient and avoid nocebo (Finniss et al., 2010; Colloca and Finniss, 2012).

5. Implications for research: design placebo and nocebo trials

The creation of an adequate trial design remains a challenge in placebo and nocebo research (Enck et al., 2011; Vase et al., 2015). Researchers should be aware that the management of the contextual factors is linked to their goals. Limiting the therapeutic relationship and the ritual around the treatment favours immersion of the specific effect of the therapy (Haas et al., 2010, 2014; Salsbury et al., 2014). In contrast, the administration of an active therapy increases the therapeutic alliance and the healthcare interaction can help to reveal the role of the context in the modulation of the patient's outcome (Suarez-Almazor et al., 2010; Fuentes et al., 2014). Much of the information presented in this paper does not result from RCTs assessing the effectiveness of individual contextual factors, but it is extrapolated from qualitative research and patient interviews. Therefore, there is a strong need for translational research with significant clinical impact (Colloca and Miller, 2011a). Several lines of investigation are a priority such as: the effect of the single and combined contextual factors on the therapeutic outcome, the PTs' knowledge and expertise about placebo and nocebo effect, the patient's perspective about the role of the contextual elements in influencing the outcome and the identification of psychological and genetic traits of placebo responders.

6. Conclusion

The difference in clinical success between two different PTs, both practicing with reference to the scientific evidence and application of the clinical guidelines lies in the different level of implementation of the “art” component of the profession. This is probably mostly due to behaviours that have relevant effects on the clinical outcome through placebo or nocebo phenomenon. The possibility of adopting knowledgeable, expert and ethical strategies to enhance placebo and avoid nocebo offers a valuable opportunity for every PT to enrich their therapeutic toolbox.

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