Neuroscience 258 (2014) 332–339

BEHAVIORAL AND NEUROPHYSIOLOGICAL INVESTIGATION OF THE INFLUENCE OF VERBAL SUGGESTION ON TACTILE PERCEPTION

M. FIORIO, [a*†] **S. RECCHIA,** [a,b*†] **F. CORRÀ** [a] **AND M. TINAZZI** [a]

[a] *Department of Neurological and Movement Sciences, University of Verona, I-37131 Verona, Italy*

[b] *Multifunctional Center "Don Calabria", I-37138 Verona, Italy*

Abstract—Recently we demonstrated that it is possible to influence tactile perception by applying a placebo manipulation consisting of verbal suggestion and conditioning and that this influence is associated to changes in the late components (N140 and P200) of somatosensory-evoked potentials (SEPs) (Fiorio et al., 2012). Due to the powerful effects of words in changing symptoms perception in the clinical domain, aim of this study was to investigate whether even in the tactile modality, perception can be changed by the mere use of persuasive words in a specific context. To this purpose, we adopted the same experimental setting of our previous study, apart from the conditioning procedure. A group of subjects (experimental group) has been verbally suggested about the effect of an inert cream in enhancing tactile perception, while a control group was informed about the inefficacy of the cream. In order to unveil the neurophysiological underpinnings of this effect, we compared the amplitude of late SEPs (P100, N140, P200), before and after treatment. Results showed that the experimental group did not perceive an increase of tactile sensation after the treatment and no modification occurred in the late SEPs. This study proves that verbal suggestion alone is not sufficient to induce enhanced tactile perception (at least with this experimental setting), suggesting that a conditioning procedure may be necessary in the tactile modality. The absence of changes in the late SEP components could reflect the lack of strong expectation following the placebo procedure.

Key words: placebo effect, expectation, verbal suggestion, tactile perception, somatosensory-evoked potentials.

INTRODUCTION

It is known that beliefs and expectations, associated with a therapeutic process, can influence human health (Colloca and Miller, 2011). In this way "*[. . .] we can influence our health outcomes by changing our mind*" (Wager and Nitschke, 2005). In recent years, increased attention has been devoted to placebo manipulations and especially to the clinician's verbal instructions necessary to induce a clinical benefit in the patient (Di Blasi et al., 2001; Benedetti, 2002; Colloca and Miller, 2011). Placebos have been defined as set of "*words, rituals, symbols and meanings*" that can change the brain of the patients (Benedetti et al., 2011). The effects of a placebo strongly depend on the way the information about the treatment is conveyed and on the environmental factors, such as social and sensory stimuli present in the context in which the treatment is applied (Di Blasi et al., 2001; Benedetti, 2002). Namely, the placebo effect obtained by administering a sugar pill, as commonly observed, is not in the sugar itself but rather in the symbolic significance of the pill (Benedetti, 2009). Hence, verbal and non-verbal interactions between the patient and the physician may affect the perception of treatment efficacy, which in turn may influence patient's expectations of benefit, and also the clinical outcome, even without the administration of active treatments (Brody, 2000; Benedetti, 2002). As stated by Benedetti et al. (2011): "*A real placebo effect is a psychobiological phenomenon occurring in the patient's brain after the administration of an inert substance, or of a sham physical treatment such as sham surgery, along with verbal suggestion (or any other cue) of clinical benefit*" (Benedetti et al., 2011).

The context in which a treatment is administered acts on the recipient's brain by means of unconscious and conscious mechanisms (Benedetti et al., 2003; Benedetti, 2009). More precisely, unconscious mechanisms are mainly based on learning processes including classical conditioning in which the frequent association between a conditioned stimulus (e.g., the color of a pill) with an unconditioned stimulus (the active substance of the pill), results in a conditioned response which is produced by the conditioned stimulus alone. Conversely, conscious mechanisms involve cognitive functions, like expectation and anticipation of benefit, belief and hope (Benedetti et al., 2003; Benedetti, 2009). Several studies demonstrated that both these mechanisms work in influencing the perception of painful stimulation (Montgomery and Kirsch, 1997;

*Corresponding authors. Addresses: Department of Neurological and Movement Sciences, University of Verona, Via Casorati, 43, I-37131 Verona, Italy. Tel: +39-0458425133; fax: +39-0458425131 (M. Fiorio). Multifunctional Center "Don Calabria", Via San Marco, 121, I-37138 Verona, Italy. Tel: +39-0458184208; fax: +39-0458184200 (S. Recchia).

E-mail addresses: mirta.fiorio@univr.it (M. Fiorio), serena.recchia@centrodoncalabria.it (S. Recchia).

† These authors contributed equally to this work.

Abbreviations: ANOVA, analysis of variance; BAS, Behavioral Activation Scale; BIS, Behavioral Inhibition Scale; LOT-R, Life Orientation Test-Revisited; NRS, Number Rating Scale; SEP, somatosensory-evoked potential; STAY, State–Trait Anxiety Scale.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.11.033

Benedetti et al., 2003; Price et al., 2008), as well as in modulating symptoms in the clinical domain. Knowledge is much less advanced with regard to the functioning of these mechanisms in other sensory modalities, different from pain. In a recent work (Fiorio et al., 2012), by applying a placebo-like manipulation, we demonstrated for the first time that similar effects can be obtained even in the tactile modality. More precisely, subjects who have been verbally influenced and surreptitiously conditioned about the effects of an inert cream in enhancing tactile sensation declared to feel the same tactile stimulus as being stronger in intensity after treatment than before. This effect was associated to changes in late somatosensory-evoked potential (SEP) components (N140 and P200), which reflect cognitive processing of sensory signal, whereas early SEPs (P14, N20, P27, P45, N60), which are sensitive to stimulus intensity, were not modulated by the procedure. That study proved that placebo effects can be obtained even in the tactile modality, by applying a procedure based on both conscious (verbal suggestion) and unconscious (conditioning) mechanisms (Fiorio et al., 2012). Whether similar behavioral and neurophysiological effects in the tactile modality could be observed even by applying verbal suggestion alone is still unknown. Aim of the current study is to investigate whether the specific verbal information related to a treatment can be sufficient in influencing tactile perception and to unveil the neurophysiological correlates of this effect. To this purpose we adopted the same experimental setting used in our previous study (Fiorio et al., 2012) in order to compare exactly the same situations with and without conditioning.

EXPERIMENTAL PROCEDURES

Subjects

A total of 24 healthy right-handed subjects participated in the experiment and were randomly assigned to two groups: 14 subjects (11 female; mean age 25 ± 3.5) have been exposed to a placebo-like procedure (experimental group) and other 10 subjects (six female; mean age 30 ± 3) served as control (control group). Subjects did not suffer from any pathological condition and none of them took any kind of drugs or was under medication. At the time of enrollment, the subjects were informed that we were collaborating with a pharmaceutical company to study the neurophysiological effects of a newly developed cream.

Procedure

The experiment took place in a silent and darkened room to facilitate the relaxation and encourage concentration and attention. Subjects were lying on a bed and they were told to relax, with eyes closed, throughout the recording sessions. The task was to judge the perceived intensity of electrical stimulation (constant current square-wave pulse of 0.2 ms) delivered on the right index finger by means of ring electrodes. To express their judgment, subjects were given a Number Rating Scale (NRS) ranging from 0 (no sensation at all) to 10 (very strong sensation). The value 0 corresponded to intensity of 0 mA, whereas the value 10 was determined for each single subject at the beginning of the experiment, by means of the method of limits, and corresponded to the intensity of stimulation just below the pain threshold.

As described in our previous study (Fiorio et al., 2012), the procedure consisted of three sessions: baseline recording, experimental manipulation (consisting in the application of treatment and verbal suggestion about its effects) and final recording (Fig. 1). In order to rule out any confounding effect due to adaptation/sensitization of the somatosensory system, subjects' tactile threshold was monitored throughout the experimental sessions (before baseline recording, after baseline recording and after final recording), by means of the method of limits (see previous study for further details Fiorio et al., 2012).

The baseline recording session consisted of two runs of 100 electrical stimuli each. During each recording session, in addition to the electrical stimulation, mechanical stimuli (about 10 stimuli in each run, as in Garcia-Larrea et al., 1991) were concurrently applied manually over the same finger by means of a gauze ball and the subject was required to count them silently. This procedure allowed us to be sure that subjects maintained a high attentional level toward the electrically stimulated finger. Accuracy in counting the mechanical stimuli and tactile threshold was checked at the end of the recording session.

After the baseline recording there was the experimental manipulation consisting in the application of a Vaseline cream on the right index finger. The cream was applied and carefully removed after 5 min by an experimenter wearing gloves and a white coat. The experimental group was told that the cream was a new active treatment capable of increasing tactile sensation and under ongoing experimental investigation for potential clinical use in stroke patients. The experimenter paid special attention to the words and to be more natural as possible while answering any curiosity raised by the subjects. This procedure has been used to verbally influence (verbal suggestion) the subject's belief and to induce an expectation of increased tactile sensation following the treatment. Conversely, the control group has been informed of the real, inefficient, nature of the treatment and was therefore told that the cream had no effect at all. Even in this case, the experimenter tried to naturally answer the questions raised by subjects.

After having removed the cream, the ring electrodes were positioned again and the final recording session was carried out following the same procedure as in the baseline session (i.e., electrical stimulation together with the mechanical touches). Also in this case, at the end of the session, subjective sensation judgments with the NRS, the number of mechanical touches and the tactile threshold were measured again.

In order to assess whether personality traits and states could influence the response to a placebo-like