Neuroscience 217 (2012) 96–104

ENHANCING NON-NOXIOUS PERCEPTION: BEHAVIOURAL AND NEUROPHYSIOLOGICAL CORRELATES OF A PLACEBO-LIKE MANIPULATION

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Abstract—Sensory perception can be influenced by cognitive functions like attention and expectation. An emblematic case of this is the placebo effect, where a reduction in pain perception can be obtained by inducing expectation of benefit following a treatment. The current study assessed the behavioural and brain activity correlates of a placebo procedure inducing an enhancement of non-noxious somatic sensation. An experimental group was verbally suggested and surreptitiously conditioned about the effect of an inert cream in enhancing tactile perception, while a control group was informed about the actual inefficacy of the cream. Both groups received non-noxious electric shocks activating A-Beta fibres on the right index finger, before and after application of the cream in the same site. The behavioural and neurophysiological effects of this procedure were measured by a numerical rating scale of subjective perception and by recording cortical and subcortical somatosensory-evoked potentials (SEPs). Although the intensity of stimulation was physically identical in the two sessions, the experimental group reported stronger tactile sensation after cream treatment than before. In parallel, the experimental group showed enhanced somatosensory cortical responses (N140, P200) after treatment, whereas subcortical and early-cortical SEP components did not change. We suggest that these findings reflect top-down modulation on tactile perception probably due to an interplay between expectation and attention and might rely on interactions between prefrontal and parietal brain regions.

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Abbreviations: NRS, numerical rating scale; SEPs, somatosensory-evoked potentials.

Key words: expectation, placebo effect, somatosensory evoked potentials, attention, somatosensory perception.

INTRODUCTION

The perception of the external world is modulated by an individual's own theories, experiences, beliefs and expectations. Hence, the same physical stimulus can be perceived differently depending on the subjective beliefs. This phenomenon has inspired marketing actions deployed to modulate the pleasantness of a consumable (Shiv et al., 2005; Plassmann et al., 2008), as well as medical actions addressed to implement the beneficial effect of a treatment (Kaptchuk, 1998).

In the clinical domain, a recipient's expectation that a benefit will follow a treatment alleviates symptoms even when the treatment is completely inert (the so-called ''placebo effect''). Under ''placebo'' we mean all those words, symbols, contexts and beliefs that accompany the administration of a treatment and that can induce psychological, neurochemical and neuroanatomical changes in the recipient's brain, so as to determine an improvement in the expression or the perception of a variety of signs and symptoms, including pain (Kaptchuk et al., 2009; Benedetti et al., 2011).

Similar influences on pain perception can be obtained also in experimental conditions. In this regard, analgesic (placebo) or hyperalgesic (nocebo) effects can be induced following painful stimulation if the subjects believe that a treatment can respectively reduce (Benedetti et al., 1999) or increase (Benedetti et al., 1999; Colloca et al., 2008a) pain. When it comes to the *non-noxious* somatosensory sensation, while changes in perception have been described by directing attention towards, or away from, a somatic stimulus, or by expecting its contact with the body (Blakemore et al., 1999), it remains unknown whether similar changes may be obtained by simple persuasion that a treatment has the power of making the stimulus feel stronger (e.g. by using a placebo-like procedure). The twofold aim of this study was therefore: (i) to investigate whether expectation of an enhanced somatosensory perception increases subjects' intensity judgements, and (ii) to determine whether such subjective increase is paralleled by objective changes in somatosensory responses (i.e. brain potentials).

To these purposes, we applied a placebo-like manipulation by suggesting subjects about the effect of an inert cream in enhancing tactile sensation. Before and after

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http://dx.doi.org/10.1016/j.neuroscience.2012.04.066

this procedure, we stimulated the subjects' hand with non-noxious electrical shocks causing a tactile-like sensation, purely driven by A-Beta afferents. This approach allowed us to precisely control the intensity of stimulation and to maintain sensation within a non-noxious range. We recorded both perceptual subjective ratings and cortical/subcortical somatosensory evoked potentials (SEPs), the latter being analyzed at multiple levels, from peripheral (spinal and brainstem) to primary, second sensory and associative cortices, so as to encompass sensory and cognitive processing of the somatosensory information.

EXPERIMENTAL PROCEDURES

We recruited a total of 43 healthy volunteers. Since subcortical, primary cortical and associative cortical SEPs need different stimulus rates to be optimally evoked, subjects were randomly assigned to two experiments, characterized by the same procedure but different stimulus frequencies. The groups were made of different subjects.

Experiment 1. Subcortical and early-cortical SEPs

Sixteen subjects participated in Experiment 1. Among these, nine subjects (seven female, mean age 29.7 ± s.d. 8.2) belonged to the experimental group and seven subjects (five female; mean age 31.9 ± 4) entered the control group. The two groups received different information regarding a treatment (see below for details and Fig. 1). Frequency of stimulation was set at 2 Hz to evoke optimally subcortical and early-middle SEPs (Yamada et al., 2004; Cruccu et al., 2008) up to 60 ms post-stimulus (components P14, N20, P27, P45, N60). These components represent an initial elaboration of the sensory signal; they are influenced by external factors such as stimulus intensity and location (Desmedt and Tomberg, 1989; Allison et al., 1992), but also by spatial-selective attention (Desmedt and Tomberg, 1989; Zopf et al., 2004; Schubert et al., 2008).

Experiment 2. Late-cortical SEPs

Twenty-seven subjects participated in Experiment 2. Fifteen subjects (six female; mean age 26 ± 5.2) entered the experimental group and 12 subjects (nine female; mean age 32.1 ± 5) served as control group. Frequency of stimulation was set at 0.9 Hz (Yamada et al., 2004; Cruccu et al., 2008) to evoke optimally late SEPs (P100, N140, P200). These long-latency components are related to higher-order elaboration of the sensory information (Desmedt and Tomberg, 1989; Nakajima and Imamura, 2000). In particular, the amplitude of N140 is influenced by the execution of cognitive tasks, independently from stimulus intensity, suggesting that it is modulated by endogenous factors related to psychological functions (Nakajima and Imamura, 2000). N140 is also highly sensitive to the spatial orienting of attention towards the stimulated body part, whereas it is strongly suppressed when attention is not required (Garcia-Larrea et al., 1995).

The study was approved by the Local Ethics Committee, and informed consent was obtained from all participants prior to the study. Participants were naïve to somatosensory evoked potentials, did not have neurological or psychiatric problems and did not receive any medication prior to examination. After experiment completion, participants were informed about the aims of the study.

Procedure

In the two experiments and in all the groups, the procedure consisted of three sessions: (i) baseline recording session; (ii) experimental manipulation (consisting of treatment application and a conditioning procedure), and (iii) final recording session (Fig. 1). The variables assessed were subjective perceptual judgements and brain responses before and after treatment, that is in the baseline and the final sessions.

Subjects lay relaxed on a bed, with eyes closed, while being stimulated on the right index finger throughout the recording sessions. Stimuli consisted of constant current square-wave pulses of 0.2-ms duration delivered through ring electrodes. After determining the subject's tactile threshold (see below), trains of stimuli were delivered at intensity three times this threshold, which allow obtaining SEPs of good amplitude and non-noxious character (Lesser et al., 1979; Tsuji et al., 1984; Cruccu et al., 2008). Tactile threshold was measured with the method of limits, by delivering a single electrical stimulus on the finger and alternating two

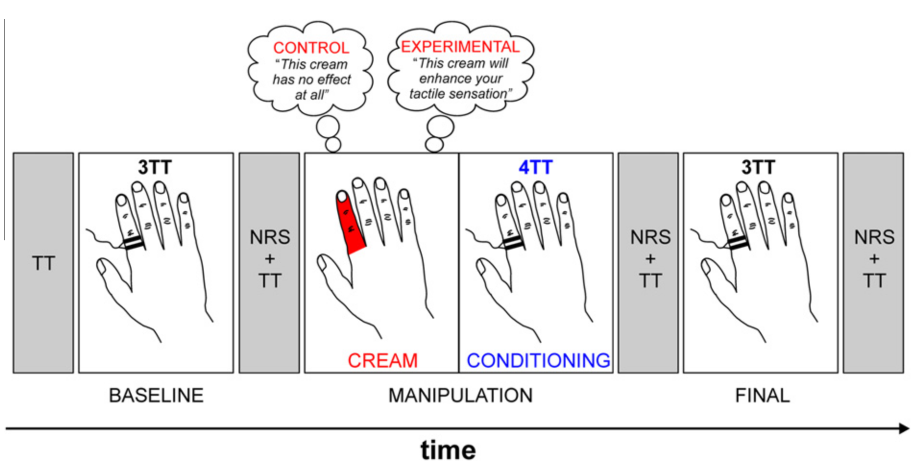

Fig. 1. Schematic representation of the experimental procedure. SEP recording sessions were interleaved by measurements of the tactile threshold (TT) and the subjective perceptual judgements (NRS). In the baseline and final recording sessions intensity of stimulation was set at three times above the TT. In the experimental manipulation, after treatment application (cream) and verbal instruction (different in the two groups), intensity of stimulation was surreptitiously set at four times above the TT (conditioning). SEP amplitude and latency recorded in the final session have been compared with those recorded in the baseline session. Since the intensity of stimulation was equal in the two sessions, any change in SEP amplitude or latency should be ascribed to the experimental manipulation.