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Blink reflex in subjects with different hypnotizability: New findings for an old debate

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HIGHLIGHTS

- Blink Reflex (BR) is an indicator of dopamine mediated attentional engagement.
- We found similar BR (with and without cue) in high and low hypnotizable subjects.
- The associated heart rate (HR) "turbulence" was different in the two groups.
- The Behavioral Inhibition/Activation System accounts for part of the HR differences.

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ABSTRACT

Hypnotizability is associated with attentional characteristics whose neurophysiological bases are still under debate. Aim of the study was the assessment of possible hypnotizability-related differences in blink reflex (BR) which has a nociceptive component, is sensitive to attentional-emotional traits and states and is modulated by the brain dopamine content.

In 10 high (*highs*) and 10 low hypnotizable participants (*lows*) BR was induced by electrical nociceptive stimulation of the right supraorbital nerve in the absence (noW) and in the presence of a visual cue preceding the electrical stimulation by 0.1 ms (W01) and by 1 ms (W1). The studied variables were: the amplitude of BR components (R1, R2, R3), the amplitude of the quick change (TO) of heart rate ("turbulence") induced by stimulation and its recovery slope (TS), the role of the Behavioral Inhibition/Activation System (BIS/BAS) in the variability BR and cardiac turbulence.

Repeated measures ANOVA did not show any significant difference between *highs* and *lows* in blink reflex. TO indicated stimulation related HR increase in *highs* and decrease in *lows*, TS was larger in *highs*. BIS and BAS accounted for the warning effects on the BR amplitude and modulated the hypnotizability and warning effects on TO and TS. Findings do not support dopamine based hypnotizability-related attentional abilities. In contrast, they indicate that hypnotizability modulates the short-lasting cardiac response to electrical nociceptive stimulation.

1. Introduction

Hypnotizability, or hypnotic susceptibility, is an individual trait measured by scales which predicts the proneness to accept suggestions [20,26]. It is associated with characteristic cortical connectivity [13,27] and dynamics [43] and with a number of correlates in the sensori-motor and cardiovascular domains in the ordinary state of consciousness and in the absence of specific suggestions [55]. In fact, it can be defined as "a physiological trait with peculiar cortical, sensorimotor and cardiovascular characteristics, associated with the ability to alter the subjective experience and (most of) its physiological correlates according to suggestions' contents" [60].

For decades the attentional abilities [9,32] of highly hypnotizable individuals (*highs*) have been attributed to higher brain dopamine content induced by low activity of the *highs*' Catechol-*O*-Methyl-Transpherase (COMT) depending on Val Met polymorphism [52]. This hypothesis has been challenged by more recent studies denying any hypnotizability-related difference in COMT Val Met polymorphism [10,51].

In addition, reports on spontaneous blinking [35–37], an attention indicator, are inconsistent. In fact, in resting conditions a few authors

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found it lower in highs than in low (lows) and medium hypnotizable participants [38], whereas others found it higher [18].

The blink reflex (BR) is a trigeminal reflex elicitable by electrical stimulation of the supraorbital nerve [8] consisting of an ipsilateral, olygosynaptic, short latency component (R1, latency 10–15 ms) and of 2 bilateral, polysynaptic later components (R2, R3) with a latency of 30–40 and 70–90 ms, respectively. The three components are separately controlled, as pontine pathways sustain R1 while medullary circuits are involved in R2 and R3. The latter wave has a partially nociceptive origin and exhibits the highest threshold (see [50]). BR is modulated by attention and emotion, reduced in parkinsonism and restored by dopamine supplementation [5–7], increased in Huntington disease [69] and by lesions of the piramidal tract [63,67]. It is considered a good indicator of brain dopamine content, although findings obtained in patients may have been biased by drugs intake and by the ongoing pathology.

Cuing nociceptive stimulation reduces the reactions to aversive stimuli (prepulse inhibition) by increasing their predictability [29,40,41]. In particular, a visual pre-pulse cue preceding electrical stimulation of the supraorbital nerve by 0.1 s or by 1 s decreases the amplitude of R2 and R3 without changing R1 [50], whereas an auditory cue causes facilitation of the R1 component at an interstimulus interval of 40–100 ms and inhibition of R2 and R3 at interstimulus intervals beyond 70 ms [9,29,53]. Prepulse inhibition of BR [12] is considered an indicator of the efficacy of a warning signal in engaging attention. It is reduced in schizophrenia and other frontostriatal syndromes [34,46,47]; in highs it has been found lower than in lows by some authors [39] and higher by other authors [14,15].

Since BR has also nociceptive components (R3), it may be associated with a cardiac defence response [49] and modulated by the activity of the Behavioral Inhibition/Activation System (BIS/BAS).

Several reports indicate that hypnotisability is associated with peculiar cardiac and vascular control. The former is characterized by a more pronounced parasympathetic activity in resting highs [59] and a lower sympathetic activation in standing highs [56,57]; the latter consists of larger endothelial nitric oxide availability in conditions reducing it in the general population such as mental stress and pain [30,31]. No significant differences have been found between highs and lows in heart rate (HR) and heart rate variability during tonic nociceptive stimulation [48,56–58,61]. However, short-lasting nociceptive stimulation could induce different cardiac responses. These will be revealed by indices such as the HR "turbulence" [1–3,62] which is able to detect quick and short-lasting HR changes (see Methods).

The BIS/BAS activity is based in limbic circuits and sustains avoidant/approaching behaviors, respectively [25,21]. The Inhibition System (BIS) reacts to novelty/punishment/non-reward, is associated with enhanced attention/arousal, is involved in negative affect, harm avoidance, conflict monitoring, behavior inhibition and anxiety disorders. The Behavioral Activation System (BAS) is activated by appetitive stimuli, potential reward, anticipatory pleasure and drive toward positive experiences (for review, [16]). BISBAS interacts with hypnotizability in the efficacy of pain imagery [58,61], pain modulation and associated cortical dynamics [42].

The aim of the present study was to measure the peak-to-peak amplitude of the three BR components, the concomitant cardiac effects of the stimulation and their possible modulation by BISBAS in *highs* and *lows*.

2. Experimental procedures

2.1. Subjects

The study was performed according to the Declaration of Helsinki and approved by the local Ethics Committee. Participants were 20 healthy volunteers (age, 20–32 years) randomly selected among those registered in the database of Lab of Cognitive and Behavioral Neuroscience of Pisa University. Their hypnotic assessment had been performed according to the Stanford Hypnotic Susceptibility Scale, form A [70] between 2010 and 2014. Their hypnotizability score was ≤4 out of 12 and ≥8 out of 12 for *highs* and *lows*, respectively. The selected subjects were −10 highly hypnotizable individuals (*highs*, 5 females) and 10 low hypnotizable subjects (*lows*, 6 females) – declared no drug intake. They were informed that no hypnotic induction will be performed. On the day of the experimental session they signed an informed consent and completed the BISBAS questionnaire [11].

2.2. Experimental session

Experimental sessions were scheduled between 2 and 5 p.m. and lasted approximately 90 min, at least 3 h after food and caffeine/alcohol containing beverages. Participants were prepared for EMG and ECG acquisition. They were comfortably seated in an arm-chair with trunk and head supported in a semi-darkened, sound attenuated room and were asked to fixate a point at eye level, 90 cm far from them, where a red light (duration = 100 ms) may appear. Electrical stimuli were administered in the absence of visual warning (12 stimuli, noW), in the presence of visual warning preceding the electrical stimulus by 0.1 s (12 stimuli, W01) and preceding it by 1 s (12 stimuli, W1). The interstimulus intervals varied between 40 and 70 s. In each participant the stimulus intensity was double than the nociceptive threshold. Warning conditions (noW, W01, W1) were randomly presented.

2.3. Data acquisition and processing

2.3.1. EMG

Electrical single pulse (duration = 200 ms) were delivered by an isolated, constant-current stimulator (Digitimer model DS7A) driven by a Labview software prepared ad hoc to the supraorbital right nerve through Red Dot consumable electrodes (cathode 1 cm above the emergence of the supraorbital nerve, anode 2 cm above). Perceptive and nociceptive threshold were assessed. The current intensity applied in each participant to elicit the R3 wave was double than the nociceptive threshold. The EMG signal was recorded through similar electrodes placed on the left and right medial part of the orbicularis inferior muscle and acquired by a Neuroscan System. The time of occurrence of the visual cue with respect to the electrical signal was marked on a separate channel of the recording device. The EMG signal was sampled at 1000 Hz and stored for offline analysis. Blink waves detection (R1, R2, R3) and the peak-to-peak amplitude measurement (post stimulus intervals for R1: 1–20 ms; R2: 20–40 ms; R3, 60–100 ms) were performed through a Labview software prepared ad hoc. Off line analysis allowed to identify the various warning conditions (noW, W01, W1) and to analyse the EMG and ECG signals in three intervals (ms 1–20, 20–40 and 60–100 after the electrical stimulation) in order to detect the R1, R2 and R3 peaks.

2.3.2. ECG

Preprocessing involved baseline wander removing by linear filtering and stimulus induced artefactual wave cancelling by Singular Value Decomposition [24]. On pre-processed ECG records, QRS detection was performed according to earlier studies recommendations [65]. For each warning condition (noW, W01, W1), an RR intervals sequence was constructed by including 2 RR intervals preceding the visual cue and 5 RR intervals following the RR interval in which the electrical stimulus occurs. These sequences, which were beat index synchronized on the stimulus, were averaged to obtain a mean RR intervals sequence.

Two parameters were considered to characterize quick RR changes ("turbulence") induced by the stimulus [1–3,62]: Turbulence Onset (TO) and Turbulence Slope (TS). TO characterizes the prompt RR change occurring after the stimulus and is defined as the normalized difference:

$$TO_{onset} = \frac{(RR_1 + RR_2) - (RR_{-4} + RR_{-3})}{(RR_{-4} + RR_{-3})} * 100$$