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Baroreceptor activation attenuates attentional effects on pain-evoked potentials

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ABSTRACT

Focused attention typically enhances neural nociceptive responses, reflected electroencephalographically as increased amplitude of pain-evoked event-related potentials (ERPs). Additionally, pain-evoked ERPs are attenuated by hypertension and baroreceptor activity, through as yet unclear mechanisms. There is indirect evidence that these two effects may interact, suggesting that baroreceptor-related modulation of nociception is more than a low-level gating phenomenon. To address this hypothesis, we explored in a group of healthy participants the combined effects of cue-induced expectancy and baroreceptor activity on the amplitude of pain-evoked ERPs. Brief nociceptive skin stimuli were delivered during a simple visual task; half were preceded by a visual forewarning cue, and half were unpredictable. Nociceptive stimuli were timed to coincide either with systole (maximum activation of cardiac baroreceptors) or with diastole (minimum baroreceptor activation). We observed a strong interaction between expectancy and cardiac timing for the amplitude of the P2 ERP component; no effects were observed for the N2 component. Cued stimuli were associated with larger P2 amplitude, but this effect was abolished for stimuli presented during baroreceptor activation. No cardiac timing effect was observed for un-cued stimuli. Taken together, these findings suggest a close integration of cognitive–affective aspects of expectancy and baroreceptor influences on pain, and as such may cast further light on mechanisms underlying mental and physiological contributions to clinical pain.

1. Introduction

Pain expectation mobilises attentional resources toward relevant external and internal stimuli facilitating adaptive behavioral and physiological responses. Attention modulates both subjective experience [5] and neural correlates [42] of pain, directing attention toward pain, relative to non direction or distraction, and increases pain-evoked ERP amplitudes [8,34,50,75,76]. Similarly, both hypnotic suggestion and expectations about pain modulate electroencephalographic [17] and functional imaging indices of nociceptive processing [41,68]. Thus the neural responses that track subjective pain [14,18,43] do not simply reproduce energy delivered by nociceptive stimuli, but are shaped by cognitive and affective processes [41,55].

Nociceptive processing is also influenced by visceral state. Even within the short timeframe of the cardiac cycle, nociceptive stimuli can be attenuated by discharge of cardiac and arterial baroreceptors, activated naturally at systole by phasic ejection of blood from the heart [3,13,35]. Experimentally, increasing baroreceptor discharge through artificial stimulation (phase related external suction, PRES, over the neck in the carotid region [23,27,59]) typically reduces subjective pain ratings [4,11,22,45,54], without necessarily affecting pain detection thresholds [22,45]. Baroreceptor activity similarly modulates neural signatures of pain processing: PRES, coupled to baroreceptor activation occurring naturally during cardiac systole, engenders a negative shift in pain-evoked ERPs [60], and timing nociceptive stimuli in relation to natural systolic baroreceptor discharge influences the amplitude of the N2 and P2 components of pain-evoked ERPs [4,11,26,54]. Baroreceptor discharge also influences skeletomotor [59] and autonomic reflexes to nociceptive stimulation, inhibiting activity in sympathetic nerves supplying skeletal muscles (muscle sympathetic nerve activity; MSNA) [19], an effect associated with attenuated blood pressure responses to pain [20,21,39,72]. Thus nociceptive processing can be modulated by baroreceptor activation, as evidenced by alterations in subjective reports, pain-evoked potential amplitudes and autonomic reactions.

Influential theories suggest a central role of visceral afferent information in emotion and motivation [15,16,58], yet it is unclear

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if baroreceptor influences extend beyond cardiovascular homoeostasis or low-level sensory gating. Nociceptive processing provides a unique window to explore how baroreceptor activity might interact with cognitive and motivational functions. Of direct relevance is the observation by Donadio and co-workers that *infrequent* nociceptive stimuli presented during baroreceptor discharge have the greatest selective impact on autonomic reactions (enhancing MSNA inhibition without altering sympathetic skin responses). Moreover, MSNA inhibition rapidly habituates if stimuli are repeated over five consecutive cardiac cycles [20]. One interpretation is that the initial nociceptive stimulus carries attentional salience, amplifying baroreceptor inhibition of MSNA, but subsequent stimuli lose salience and have diminished baroreceptor-related effects. Alternatively, the effect may emerge from refractory characteristics of homoeostatic neurons that specifically fatigue MSNA inhibition across consecutive cardiac cycles.

The current study, extending earlier neuroimaging work [39], was motivated to examine the interaction between attentional salience and phasic visceral effects in nociception. We modulated expectancy by embedding nociceptive stimuli within a visual task, to dissect attentional and baroreceptor influences. We hypothesized that if expectancy and attention, rather than physiological habituation, modulate the baroreceptor gating of pain responses [20], then the baroreceptor influence on the pain-evoked ERPs would be different between expected and unexpected pain, suggesting that attentional effects on central nociception are mechanistically dependent on visceral state.

2. Methods

2.1. Participants and recording procedure

Eleven adults (age 28 ± 9.8 years) participated in the experiment after providing written informed consent. To avoid recognized gender differences in nociceptive processing [7,31] we restricted our sample to female participants. All participants were medication free at the time of testing and reported no history of psychiatric or neurologic disorders. The study was approved by the Brighton and Sussex Medical School (BSMS) research governance and ethics committee. All recordings were performed in a psychophysiology laboratory, with the participant comfortably seated in a dimly-lit, quiet room while the experimenter remained nearby.

2.2. Physiological and EEG recordings

Beat-to-beat blood pressure was recorded through a finger cuff applied on the left hand using the volume-clamp method of Peñáz as implemented by the Finometer device (Finapres Medical Systems BV, Arnhem, The Netherlands). Three lead ECG recordings were made with Ag–AgCl electrodes positioned according to Einthoven's triangle, standard lead I configuration, using an isolated pre-amplifier (model 1902, CED Ltd., Cambridge, UK). The electrocardiogram (ECG) and blood pressure signals were digitized through a 'power1401' data acquisition device (CED) and recorded on a PC running the Spike2 version 7 software.

The electroencephalogram (EEG) was recorded through 19 electrodes positioned according to the 10/20 system and held in place by a lycra cap (Electro-Cap Inc., Eaton OH, USA), using a Mindset MS-24 EEG system (Nolan Computer Systems, Inc., Fort Morgan CO, USA) electrically isolated from all other equipment. After band-pass filtering in the 0.1–30 Hz range, signals were sampled at 512 Hz. Recordings were performed relative to a linked-ears reference, and individual electrode impedances were kept below 5 kΩ.

2.3. Experimental task

Participants performed a passive viewing task, in which four white visual shapes (square, circle, rhombus or triangle) were displayed on a black background for 300 ms by means of a CRT screen positioned at 1 m distance. They were initially shown each stimulus shape and the experimenter indicated which one, randomly chosen for each session, would be the 'target' and would therefore always be followed by a nociceptive electrical skin stimulus (see Fig. 1A–C). Targets accounted for 25% of visual stimuli. Nociceptive stimuli were timed to either coincide with the ECG R-wave or to be delivered 300 ms after it. The R-wave corresponds to the end of cardiac diastole, and therefore to relative baroreceptor inactivity. On the contrary, 300 ms after the R-wave corresponds approximately to the systole, when baroreceptor firing is maximal. In other words, in order to perform this study we did not measure the latency of baroreceptor activation with respect to the R-wave, but we assumed these timings a priori, on the basis of the convergent findings reported in existing literature [25–28,39,53].Throughout this paper, stimuli presented during the ECG R-wave are termed "baroreceptor silent stimuli" whereas stimuli presented 300 ms following the ECG R-wave are termed "baroreceptor active stimuli". The timing of the electrical stimuli was controlled by a real-time script running on the CED-power1401 unit, identifying the QRS complex with sub-millisecond temporal accuracy. Participants were informed that, in addition to the nociceptive stimuli cued by the visual target, uncued stimuli would also be presented at unpredictable points throughout the task.

A complicating factor is the possibility of expectancy-induced cardiovascular responses, since increased blood pressure during pain anticipation may attenuate pain processing [24,48,62]. Consequently, the average time between the cue and the electrical stimulus was kept brief (3.1 ± 0.3 s), corresponding to a jitter of about 10% which included the variable delay due to cardiac synchronization. Additionally, jittering the cue-to-nociceptive-stimuli interval ensured that the effect of cue-induced expectancy on the ERPs could not be confounded by synchronization of EEG rhythms potentially induced by the visual stimuli. Considering all stimuli (visual and electrical) together, the average inter-stimulus time was 2.6 ± 0.5 s; separately, visual stimuli occurred every 3.9 ± 1.7 s, and nociceptive electrical stimuli every 7.4 ± 4.5 s. We specifically ensured nociceptive stimuli were never delivered during consecutive cardiac cycles to minimise the possible refractory attenuation of baroreceptor influences. The corresponding distributions are shown in Fig. 1D.

Participants completed the task in four blocks of about 380 s each, with a pause of approximately 140 s between blocks. Painfulness ratings for the electrical-skin stimuli were verbally collected after each block on a 1 (barely identifiable as pain) to 10 (imaginary worst possible pain) scale, and averaged across blocks. The overall task duration was approximately 30 min. In total, 200 nociceptive electrical-skin stimuli were delivered, evenly balanced between the baroreceptors silent and active conditions, and between the cued and un-cued conditions.

2.4. Electrical-skin stimuli

Two standard EEG electrodes (Ag–AgCl, 5 mm radius circular cup filled with Ten20 conductive paste) separated by approximately 1 cm were attached to the right ventral wrist. Electrical-skin stimuli were delivered by means of a constant-current stimulator (DS7A, Digitimer Ltd., Glenwyn Garden City, UK), and consisted of a single square-wave pulse with 2 ms width and maximum voltage 400 V. Before starting the experimental task, stimulus intensity was determined on an individual by individual basis.