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Tonic Pain Abolishes Cortical Habituation of Visual Evoked Potentials in Healthy Subjects

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Abstract: **We investigated changes in visual cortex excitability by analyzing visual evoked potential (VEP) habituation in healthy subjects during tonic pain evoked by the cold-pressor test (CPT). We tested VEP amplitude habituation (slope of the linear regression line for N1-P1 amplitude from the 1st to 6th block of 100 sweeps) in 19 healthy volunteers during 4 experimental conditions: baseline; no-pain (hand held in warm water, 25°C); pain (hand held in cold water, 2–4°C); and the after-effects of tonic pain. During baseline and no-pain sessions, VEPs habituated normally across the 6 consecutive blocks (mean slope –.28 and –.18%), whereas during pain and its after-effects they failed to decrease (0%, and –.11%). Tonic pain induced by the CPT abolishes normal VEP habituation and the lack of habituation persists after the CPT is stopped. Tonic pain probably abolishes VEP habituation by acting on brainstem neural structures which modulate thalamo-cortical activation thereby changing visual cortex excitability.**

Perspective: ***This study shows that tonic pain alters visual cortex excitability, a brain region unrelated to pain processing. These changes probably reflect defensive strategies against pain. Extending the study from healthy volunteers to patients with migraine between attacks would offer the opportunity to investigate visual cortical excitability under conditions when baseline habituation is absent.***

Key words: *Tonic pain, visual evoked potentials, habituation, thalamo-cortical activity.*

The standard method for assessing excitability in the occipital cortex, is to record visual evoked potentials (VEPs), ie, the electrical cortical response to monocular visual stimuli. The occipital cortex is a brain region outside the pain matrix,[30] hence unrelated to pain processing. As happens with stimulation using various sensory modalities, repeated visual stimulation causes human VEP to habituate (decrease in amplitude).[11]

Habituation is a ubiquitous phenomenon observed in simple and complex neuronal circuits, from the gill-withdrawal reflex in Aplysia to the autonomic and behavioral component of the whole-of-body reflex called the orienting response in humans.[19,41] Short-term habituation is a common feature of responses to any type of sensory stimuli and is commonly defined as "a response decrement as a result of repeated stimulation".[20] Studying cortical habituation allows investigators to analyze information processing in the central nervous system (CNS), the mechanisms of learning, and ultimately the neuronal substrates of behavior.[41]

Despite intensive research over the past 30 years, the neural mechanisms underlying habituation remain poorly understood, as does the lack of habituation found in various neurological conditions.[11] In a study conducted in 1970, seeking to explain the changes in behavioral response amplitude reflected by habituation, Groves and Thompson[19] proposed the dual-process theory. This theory hypothesizes that 2 opposing processes, ie, depression and facilitation, compete to determine the final behavioral outcome after stimulus repetition.

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At synaptic level, the stimulus-response pathway interacts with an external state system represented by various tonic nonspecific and motivational circuits, including the ascending reticular activating system and related structures.[19] Among these structures are the brainstem monoaminergic nuclei, critically involved in the central processing of arousal, control of the signal-to-noise ratio generated by sensory stimuli at cortical and thalamic level, and endogenous antinociception.[25]

A long-used and validated in vivo model for studying nociception and antinociception is the cold-pressor test (CPT),[28,46,49] a procedure that induces tonic pain. To our knowledge no studies have investigated changes in the excitability of the human visual cortex during tonic pain induced in the hand. Having this information might help to understand whether and how ascending systems control cortical excitability.

Prompted by the dual-process theory on cortical habituation, in experiments designed to modulate the state system, in this study we investigated whether and how tonic pain induced in the hand by the CPT influences VEP habituation. To do so, we tested VEP amplitudes in healthy volunteers recorded in 6 consecutive blocks before, during, and after the CPT and calculated how much the VEP amplitude changed along the blocks.

Methods

Subjects

We recruited 21 healthy subjects among medical students and healthcare professionals. To avoid sex-hormone-induced effects on pain,[40] we studied women during their follicular phase (days 8 to 10 from the first day of menstrual bleeding). We excluded subjects with overt medical conditions, personal or familial history of neurological (including migraine) or psychiatric illness, as well as subjects who were unable to tolerate the CPT, and those having best corrected visual acuity < 8/10.

All participants were given a complete description of the experimental design and granted informed consent to the study, which was approved by the Ethics Committee of the "Sapienza" University of Rome, Polo Pontino.

Data Acquisition

Subjects sat in a semidark, acoustically isolated room in front of the display surrounded by a uniform luminance field of 5 cd/m^2. To obtain a constant pupil diameter, before VEP recording, each subject adapted to the ambient room light for 10 minutes. VEPs were recorded to monocular stimulation with the contralateral eye occluded. Visual stimuli consisted of full-field checkerboard patterns (contrast 80%, mean luminance 250 cd/m^2) generated on a TV monitor and reversed in contrast at a rate of 3.1/second. At the viewing distance of 114 cm, the single check edges subtended a visual angle of 15 minutes. Subjects were instructed to fixate a red dot in the middle of the screen with the contralateral eye covered by a patch to maintain stable fixation. VEPs were recorded from the scalp by means of silver cup electrodes positioned at Oz (active electrode) and at Fz (reference electrode, 10/20 system); and a ground electrode was placed on the right forearm. Signals were amplified by Digitimer D360 preamplifiers (band-pass .05–2000 Hz, gain 1,000) and recorded by a CED power 1401 device (Cambridge Electronic Design Ltd, Cambridge, UK). A total of 600 consecutive sweeps of 200 ms duration were collected and sampled at 4,000 Hz.

Cortical responses were partitioned in 6 sequential blocks of 100, consisting of at least 95 artifact-free sweeps. Responses in each block were averaged off-line (block averages) using the Signal software package version 3.10 (CED Ltd).

VEP components were identified according to their latencies from the stimulus: N1 was defined as the most negative peak between 60 and 90 ms, P1 as the most positive peak following N1 between 80 and 120 ms, and N2 as the most negative peak following P1 at between 125 and 150 ms. We measured the peak-to-peak amplitude of the N1-P1 complex. Habituation was defined both as the change in amplitude of N1-P1 recorded during the 6 blocks and the slope of the linear regression line for the 6 blocks.

Cold-Pressor Test

We induced tonic pain using a validated cold-pressor test (CPT).[35,46,49] The subjects were required to dip their right hand, to a depth of 5 cm above the wrist, in a thermo-regulated water bath for 4 minutes. The water temperature was maintained at 3 to 4°C.

Procedure

VEP habituation was evaluated in separate sessions under 4 experimental conditions: baseline, before the CPT; no-pain condition (VEPs recorded while subjects dipped their hand in the water at 25°C); pain condition (VEPs recorded 1 minute after the start of CPT); and aftereffects condition (VEPs recorded 5 minutes after the CPT ended). Pain and no-pain conditions were randomly assigned after the baseline session. To avoid possible skin receptor sensitization, after the hand was removed from the water it was dried, and subjects rested more than 20 minutes between pain and no-pain sessions. Because the no-pain condition probably does not sensitize skin receptors, after the hand was removed from the water subjects rested about 10 minutes between no-pain and pain sessions (Fig 1).

All recordings were collected in the morning (between 0900 and 1100 hours) by the same experimenter.

Subjects rated the subjective intensity of the painful sensation on an 11-point numerical scale (11P NS) scale, graded from 0 = no pain to 10 = unbearable pain.

Statistical Analysis

We used the Statistical Package for the Social Sciences (SPSS) for Windows, v15.0 (SPSS, Inc, Chicago, IL) for all analyses. VEP amplitudes recorded in all blocks were tested in a repeated-measures analysis of variance (ANOVA) with factors block and session. A regression analysis was used to disclose linear trends in VEP amplitude across blocks in each condition (slope). Paired-sample t

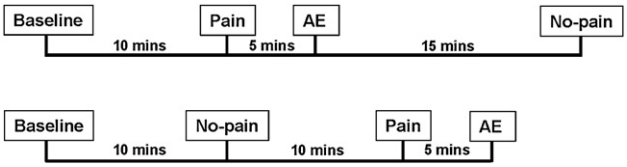

Figure 1. Revised template of the CONSORT diagram shows the flow of participants through 3 stages of the study (enrollment, intervention allocation, and analysis).

test was used to compare block 1 VEP amplitude at baseline and during pain condition.

Pearson's correlation coefficient was used to test correlations between slope of VEP amplitude linear trends and subjective measurements of pain (11 PNS scores).

P values less than .05 were considered to indicate statistical significance.

Results

Complete VEP recordings were obtained from 19 subjects (12 women and 7 men, mean ± SD age: 26.6 ± 3.4 years) (Fig 1). Two subjects (1 woman and 1 man) unable to tolerate the CPT withdrew from the study and their data were excluded from the analysis.

The 11 PNS scores for subjective pain evaluation were 7.6 ± 1.8.

ANOVA of VEP amplitude block averages disclosed a main effect for factor block ($F_{(5,360)} = 5.66$, $P < .001$), and a significant interaction of session by block ($F_{(15,360)} = 1.93$, $P = .022$). (Table 1). Linear regression analysis of VEP amplitudes recorded in all blocks differed between sessions ($F_{(3,72)} = 3.25$, $P = .02$). Post hoc analysis showed that during baseline and no-pain conditions the linear trend in VEP amplitudes decreased from block 1 to block 6 (–.28 during baseline, –.18 during no-pain; Fig 3). Conversely, during the pain condition and after effects it remained unchanged (0.00 pain condition, Fig 2) or almost unchanged (–.11 after effect; Fig 3). Paired T-test showed that the baseline block 1 VEP amplitude decreased significantly during the pain condition ($t_{(1,18)} = 3.53$, $P = .002$, Fig 3).

Pearson's test disclosed a negative correlation between the slope of the linear trend in VEP amplitude and block 1 VEP amplitude during pain ($r = -.678$, $P = .001$), and during the after-effect condition ($r = -.615$, $P = .005$). Pearson's test disclosed no correlation between the 11 PNS scores and slopes of VEP amplitude linear trends (all, $P > .05$).

Discussion

In the healthy volunteer subjects we studied, tonic pain induced by the CPT abolished the normal VEP habituation (amplitude decrease to repeated stimulation). This is to our knowledge the first report describing changes in the excitability of the human visual cortex (as measured by N1-P1 amplitude habituation) —a brain area unrelated to pain processing—during tonic pain induced in the hand.

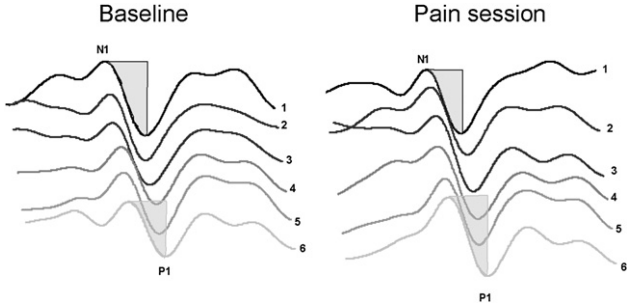

Figure 2. Representative recordings of visual evoked potential (VEP) habituation in a healthy volunteer at baseline (left) and during the cold-pressor test (right).

Current knowledge on habituation to tonic pain suggests that the lack of VEP habituation we observed during tonic pain arose from mechanisms within the CNS alone, uninfluenced by processes of receptor adaptation. In experimental models of habituation and dis-habituation, early studies on time-dependent changes in cortical responses to weak or strong somatosensory stimuli found no evidence for receptor adaptation or motor fatigue.[5–7] Hence, in their early study, Thompson and Spencer[41] introduced the specific operational definition of habituation to indicate a reversible response decrement during a stereotyped stimulus presentation, in the absence of receptor adaptation or motor fatigue.

The CPT we used in this study induces such intense pain that 2 of the 21 volunteers we studied were unable to tolerate. Morphological and functional studies in animals and humans show that tonic pain, such as that evoked by immersion of a hand in iced water, conducts specifically through peripheral Aδ and C fibers.[44,45,48] Their ascending pathways travel along the ventrolateral (crossed) and the dorsolateral (uncrossed) funicula,[3,34,44] and send direct connections to a neuronal centre localized in the bulbar reticular formation.[34,48] Other supraspinal connections include portions of the brainstem (locus coeruleus and the parabrachial nucleus),[1,12] and the forebrain (periaqueductal gray, rostroventral medulla).[47]

How tonic pain induced in the hand modulates excitability in the human visual cortex—a posterior brain area unrelated to pain processing—remains partly unclear. Ample evidence shows that tonic pain induced in remote sites can modulate the excitability of various neural circuits. For example, it inhibits spinal and trigeminal reflexes,[15,27,36,38,49] thalamic responses,[4,13,47] and cortical activity.[9,18,23,32,33] Studies of cortical function show that tonic pain induces marked changes in posterior areas. During the CPT, when subjects immerse the hand in cold water, EEG background activity changes in the posterior parietal and occipital regions.[2,8,10,17] During the first minute of immersion, EEG alpha activity decreases phasically, but subsequently recovers or even augments.[2,8] The drop in alpha-band activity—termed event-related desynchronization (ERD)[2,8] or alpha blocking—indicates that painful stimulation decreases the synchrony between cortical neuronal elements generating alpha rhythms, thereby reducing alpha-band power.[26,31] Reduced alpha power during the CPT is an

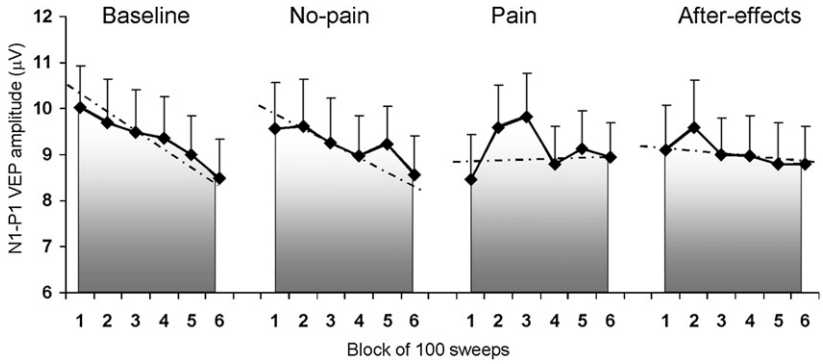

Figure 3. Visual evoked potential N1-P1 block amplitudes during the 4 experimental conditions. The dotted line represents the slope of the linear regression line.

important finding pertinent to our study, because VEPs are generated in the occipital cortex, and simultaneous EEG and near-infrared spectroscopy recordings show that low alpha-amplitude in healthy subjects is related to small oxygenation responses and reduced VEP amplitude.[22]

A VEP datum that makes the lack of VEP habituation we observed during tonic pain an even more robust and interesting finding is the significant block 1 VEP amplitude reduction between baseline and pain conditions (Fig 3). This pain-related change in VEP amplitude indicates that although our subjects underwent brain changes reducing posterior alpha power and VEP amplitude, by the time we recorded VEPs alpha power had already started to recover.[2,8]

Because tonic painful stimulation, such as that evoked by the CPT, modulates thalamic activity directly via the trigemino-thalamic and the spino-thalamic convergent neurones,[14] and indirectly by activating the caudal brainstem reticular formation which projects to the ventromedial thalamic nucleus,[13,43] its effect on EEG alpha power is conceivably mediated by the thalamus. Alpha-band rhythms arise from an interplay by thalamic relay cells with cells of the reticular nuclei and cortico-cortical reverberant loops.[24,39] An inverse relationship exists between the EEG alpha power and the level of thalamo-cortical activity.[39] Hence, the lack of VEP habituation we observed during the pain condition harmonizes nicely with the alpha band increase described during continuous EEG recordings.[2,8] We therefore suggest that the reduced VEP amplitude we observed in block 1 during pain reflects an initial increase in thalamo-cortical activation probably driven by attentional processes to pain,[29] whereas the subsequent lack of habituation reflects late inhibitory thalamo-cortical mechanisms.[2,8]

An interesting finding that merits further research was that the late mechanisms during tonic pain outlasted the painful stimulation and persisted during the aftereffects condition. The aftereffects of tonic pain on brain function last up to 10 minutes in animals,[13,34,49] and up to 30 minutes in humans.[16,18,42] They presumably reflect plastic changes in the CNS,[13,42,49] which mainly depend on the type, intensity, and modality of conditioning stimulation.[49] Aftereffects change the synaptic effectiveness in the stimulated cortex as well as long-term depression (LTD) and long-term potentiation (LTP) in experimental preparations.

In our study, block 1 VEP amplitudes invariably correlated negatively with habituation both during the pain and the aftereffects condition. This finding confirms that the induced LTD/LTP-like phenomena also depend on the state of the cortex at the time of conditioning stimulation, so that synaptic depression and potentiation correlate inversely with the level of activity in the postsynaptic neuron.

Our study suggests that tonic pain alters excitability in the human visual cortex, possibly by inducing biphasic changes, ie, an early depression followed by a late facilitation that outlasts the painful stimulation. According to the dual theory, this means that the interaction between the stimulus-response pathway (the visual system) and the external state system (ascending and descending neural systems including brainstem-thalamic circuits) also shows a biphasic time course, during which the opposing processes of depression and facilitation predominate one after the other to determine the final behavioral outcome after stimulus repetition. Because we perturbed the state system by inducing tonic pain with the CPT, we suggest that the CPT-induced changes in cortical function act indirectly when the brainstem monoaminergic nuclei activated during the first minutes of the CPT ultimately modulate thalamo-cortical circuits.[28] Because brainstem nuclei control the central arousal processing and also tune the signal-to-noise ratio generated by sensory stimuli at thalamic and cortical levels, they may also contribute to the attentional processes that initially inhibit—and to the filtering mechanisms that subsequently facilitate—the visual cortex. These mechanisms are probably intended to improve the subjects' visual performance that assists or optimizes the defensive strategies essential to initiate a rapid response in a potentially life-threatening situation.[21]

Conclusion

In conclusion, tonic pain evoked by the CPT modulates the cortical response to repeated visual stimuli by inducing an early depression and a late facilitation (loss of habituation). These changes in cortical excitability take place because the CPT activates brainstem monoaminergic nuclei that in turn modulate the activity in thalamic and cortical neurons. Changing cortical excitability during and after

pain is probably part of a complex behavioral response aimed to adopt defensive strategies against pain. Extending our study from healthy volunteers to patients with migraine between attacks would offer a unique opportunity to investigate defensive strategies against tonic pain under conditions when baseline habituation is absent.[11,37]

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