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Neural response associated with the modulation of temporal summation of second pain by affective touch

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ABSTRACT

Temporal summation of second pain (TSSP) is a phenomenon that has clinical relevance but insights into its functioning are limited. Lately, 'affective touch' (AT) has been shown to have pain relieving properties but only one study has investigated its effects on TSSP and the neural underpinnings of such interaction are unknown. In the present EEG study, thirty-six healthy participants went through three conditions where a TSSP protocol was applied in concomitance with no touch (NoT), discriminative touch (DT) and AT. A fourth no-pain no-touch condition acted as a baseline. Measures of attention during the four conditions and of pleasantness during the touch conditions were also recorded. Pain ratings were significantly lower only during the AT condition. The neural response during NoT, compared to the baseline, brought about a temporal decrease in power at delta and theta frequencies and a fronto-central increase mainly in the alpha rhythm. Adding AT to TSSP yielded, compared to NoT, a decrease in delta, theta and beta bands in midline regions at both central (Cz) and parietal (Pz) and also of gamma at Pz. Notably, DT was not associated with significant changes compared to pain alone (NoT), but a specific marked difference was found between AT and DT with the former showing a significant decrease in beta frequencies localized at Pz. While TSSP seems to be characterized by a modulation mostly of the lower frequencies, adding AT to TSSP brings a clear depression of all the major frequency bands. Additionally, the parietal beta reduction may be a biomarker of AT. Future studies can examine if such brain response can help finding a suitable intervention for TSSP-related chronic pain conditions.

Perspective: This study consolidates the idea that AT can lower pain in a TSSP paradigm and shows what are the brain (EEG) responses associated with both TSSP and TSSP modulation by AT. Given that TSSP is linked to central sensitization and that it can be used as an experimental model for chronic pain, our results pave the way for further studies into the neural mechanisms of AT-led analgesia, which can lead to future effective treatments.

Introduction

Central sensitization (CS) refers to an increase in spinal cord neuronal excitability and is characterised by augmented spontaneous neuronal activity, decrease in response threshold, increased response to suprathreshold stimuli, and enlarged receptive fields.[1,2] Such phenomenon appears to play a key role in the pathogenesis of chronic pain (CP) conditions including fibromyalgia, musculoskeletal disorders, headache, dental and neuropathic pain.[3,4] Temporal summation of second pain (TSSP), classically induced by a stimulation rate of 0.33 Hz,[5] has been referred to as a psychophysical index of the spinal 'wind-up'[6] and deemed relevant for the functional evaluation of CS.[6,7] Due to its clinical relevance, TSSP has been studied in patients,[8–12] where it shows to be abnormal,[8,13] and in pain-free subjects, as an experimental model for CP.[14–17] However, the mechanisms underlying TSSP modulation are not fully understood. Pharmacological interventions see the N-methyl-D-aspartate (NMDA) antagonists like dextromethorphan and ketamine as effective in reducing TSSP in both healthy participants and CP patients.[18,19] Behavioural interventions like aerobic and isometric exercise also show the potential to ameliorate TSSP.[20,21] Lately, it has been shown how touch, specifically the so-called "affective touch" (AT),[22] can effectively reduce TSSP, whereas a much slower ('sub-optimal') stroking induces no significant modulation of it.[16]

Although new evidence would see mechanoreceptive A-fibers contribute to the perceived intensity and pleasantness of gentle stroking,[23] AT, sometimes also referred to as "social", "sensual" or "pleasant

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touch",[24,25] classically relies on type-C unmyelinated low threshold mechanoreceptive afferents (C-LTMRs), or C-tactile (CT) fibres.[25] These fibres are solely localised in hairy skin and they have been linked to the affective feature of touch.[26] Noticeably, they preferentially respond to gentle stroking, at a speed of ~1–10 cm/s,[27,28] and their firing rate positively correlates with ratings of touch pleasantness.[24] So, if Aβ myelinated mechano-afferents sub-serve the spatial-temporal features of discriminative touch (DT),[26] CT-mediated touch operates an affective-motivational function.[29] At a neuro-anatomical level CT and C-fibres both project to the same layers of the dorsal horn of the spinal cord (laminae I/II)[30] and share the spinothalamic tract,[26,31] suggesting a possible interaction between AT and pain mediated by C-fibres. While the pain-dampening effect of concomitant afferent stimuli delivered by large myelinated Aβ fibres has been known since the 1960′s,[31] studies linking AT to analgesic effects are still scarce. The first observations that CT fibres could be involved in pain processes are recent and show a link between dynamic tactile allodynia and reduced C-tactile mediated hedonic-touch processing.[32,33] Latter indications have shown how AT is effective in reducing acute pain,[16,34–36] while mixed findings are derived from the few studies conducted so far on CP patients (see[34,37–39] for a review on the topic). In a recent study which considered TSSP as a proxy for CP, pain was significantly lower during AT compared with no touch or even DT.[16] If it is known that repeated painful electrical stimulations on the skin are associated with the emergence of a frontal negativity,[40] and that repetitive laser stimulations can lead to increased gamma band at the vertex,[41] still much remains to be discovered about the neural underpinnings of AT-led TSSP modulation. Therefore, with the present study, we aimed at revealing for the first time the EEG responses associated with both TSSP and TSSP modulation by AT.

Materials and methods

Participants

Thirty-six healthy volunteers, 12 males and 24 females, aged between 20 and 45 years (mean ± SD = 28.31 ± 6.59) were recruited for this study. All participants were right-handed (mean ±SD = 95.31 ± 9.81, range 61–100) according to the Edinburgh Handedness Inventory.[42]

Exclusion criteria comprised age range (under 18 and over 55 years), those with prior history of neurological or psychiatric disorders or with on-going chronic pain conditions (i.e. pain persisting beyond 3 months), drug intake (psychotropic drugs, painkillers, including over-the-counter medications), skin problems (especially if related to the stimulated body part) and any other health condition (e.g. traumatic injuries) that could alter pain or tactile perception.

The experimental procedures were approved by the local ethics committee and were in accordance with the Declaration of Helsinki. Volunteers received a compensation of £15 for participating in the experiment.

Design

Four experimental conditions were implemented in a within-participants, counter-balanced, design: a 'No Touch' (NoT), a 'Discriminative Touch' (DT), an 'Affective Touch' (AT) and a 'Baseline' (B) condition.

Tactile stimulation

The experiment comprised two pain + touch conditions: a 'normal' tactile stimulation ("DT") purportedly mediated by the activation of Aβ fibres, and a more pleasant tactile stimulation, deemed to trigger the CT-fibres response ("AT"). The tactile stimulation velocities were the same as those adopted in Fidanza and colleagues' study[16]: 0.3 cm/s for DT and 10 cm/s for AT. The former is considered to be sub-optimal to elicit the CT-fibres response and therefore it was used as a control tactile stimulation (i.e. in "DT"). Optimal stroking velocities are indeed considered to be within 1 and 10 cm/s, while sub-optimal velocities are 0.1, 0.3 and 30 cm/s (e.g., see[27]).

Contrary to the manual stimulation used in Fidanza's study, here we avoided possible confounding factors related to hand-touching.[43] Hence, the tactile stimulation was delivered by two opposite brushes attached to an ad-hoc (i.e. the product is not 'labelled' for the use under discussion) Lego Technic device (LEGO System A/S, DK-7190 Billund, Denmark,). The device was built in a way that the brush covered a linear path of about 15 cm on the participant's lower arm and the direction of the continuous tactile stimulation was proximal to distal (elbow to wrist). Throughout the DT condition the device stroked the dorsal side of their arm at a speed of 0.3 cm/s. For the AT condition, the stroke speed was set to 10 cm/s. The stimulation area was kept constant across the two tactile stimulation conditions.

Thermal stimulation

The stimulation paradigm that was adopted in this experiment was taken from a previous TSSP study carried out in the same lab.[16] A TSA-II Neuro Sensory Analyzer (Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel) was used to deliver heat stimuli. Trains of six heat pulses, with a stimulation frequency of 0.33 Hz, were delivered through a 30×30 mm thermode which was placed on the dorsal side of the participant's right wrist. A similar stimulation paradigm was previously adopted by Staud and colleagues.[17,44] Each pulse consisted of an ascending and descending heat stimulation, with the temperature of the thermode increasing and decreasing by 8 °C/sec. The duration of a whole stimulation cycle was 3 sec. Prior to the start of the experiment, the individual target temperature was adjusted to each individual's heat pain sensitivity and it was regulated to achieve maximal thermal TSSP ratings of 45 ± 10 after six heat pulses at 0.33 Hz.[17] Pain ratings were collected via a Computerized Visual Analogue Scale (CoVAS, 0–100 scale; Medoc Ltd.) at the end of each train of stimuli.

Subjective data

Participants' demographics data were collected through a case report form; in addition, each subject was requested to provide ratings of attention and pleasantness during the heat stimulation, as described below.

Attention ratings

Pain demands attention and it is modulated by it,[45] hence to control for possible pain modulations due to attentional fluctuations, participants were asked to provide a rating of attention right after each train of heat stimuli. The number reported by the participant referred to a 0–10 numerical rating scale (NRS), where '0′ indicated that 'my attention was not at all on the thermal stimulus but on other things, for instance the tactile stimulus' and '10′ meant that 'my attention was fully on the thermal stimulus'. So, higher ratings indicated greater attention allocated to the thermal/painful stimulus, while lower ratings indicated greater distraction. A Friedman ANOVA was planned in order to test the difference in attention allocation across all four experimental conditions.

Touch pleasantness ratings

One of the primary characteristics of AT is that it is accompanied by a pleasantness sensation.[46] Thus, right after each train of heat stimuli participants were asked to rate the perceived pleasantness relative to the tactile stimulations (both during AT and DT). Specifically, they were asked to indicate how pleasant the tactile stimulation had been spelling out a number on a 0–10 NRS, where "0" corresponded to "not pleasant"

and "10″ to "maximally pleasant". To ensure that the answers were representative of the actual experience of the participants, they were told that there were no "right" or "wrong" responses and that their answers had to be based only on their true feelings. A Wilcoxon signed-rank test was planned in order to test the difference between DT and AT conditions.

Procedure

Upon their arrival the participants were seated comfortably on a chair and confirmed their written informed consent. Then, participants were instructed on how to use the COVAS: they were told that their pain sensation may vary during the stimulation and, in case they perceived a change, they should provide a 'live' assessment of their pain, moving the slider of the COVAS to the left or to the right as their sensation changed (this way we could have a more precise assessment of all the pain peaks corresponding to each stimulus of the train). Participants were told that the extreme left of the COVAS corresponded to "no pain" and that the extreme right to the "worst imaginable pain".

Once the participant was confident with the use of the COVAS, the individual's target temperature was taken delivering 3 trains of 6 heat stimuli each. Participants were asked to place their arms on the experimental table, where a metal frame prevented them from seeing their right (stimulated) arm. The thermode was secured with an elastic Velcro strap on the right wrist on the dorsal side. The left arm was placed near the CoVAS, whereby the participants could rate their pain. Participants were then asked to look at a fixation cross placed on the table aligned with their body midline, at a distance of about 30 cm. The target temperature was set when the maximal temperature of the thermode elicited, on average, a pain rating of 45 ± 10.[17] During these preliminary trials, stimulus trains were started at 47 °C (peak pulse temperature), and after 6 pulses (i.e. one train) the participant was instructed to give the pain rating, via COVAS.

Once the thermal target was set, the thermode was temporarily removed and the 128-channel Hydrocel Geodesic Sensor EEG Net was mounted on the participants' head and connection established with the amplifier. Participants were then asked to return to their original position with their arms on the table (the right arm behind the metal frame) and the thermode was again attached to the right wrist dorsum. Once the participant felt ready, the experiment (recording) commenced.

In each experimental condition, 10 trains of 6 heat stimuli were delivered with an intertrial interval (ITI) of 30 s and the duration of each heat pulse was set to 3 seconds (1.5 s for the rise and 1.5 s for the return time). In total, every participant received 180 trains of painful heat stimuli ("NoT", "DT", "AT") plus 60 non-painful heat stimuli during the baseline ("B") condition.

For the "NoT" condition participants received the heat pulses with no concomitant tactile stimulation. During the two tactile conditions ("DT" and "AT") participants received the painful heat together with the corresponding tactile stimulation (0.3 cm/s and 10 cm/s respectively). The baseline ("B") condition consisted of heat stimuli which followed the same pattern of the painful stimuli (3 s duration, 1.5 increase, 1.5 decrease) which were not supposed to be painful, i.e. delivered at temperatures between 33 and 38 °C (that is below 40 °C[47]), but that could still be perceived by the participant.

After each train of pulses, at about 2 s from the last stimulus, the experimenter asked the participant to rate, verbally, attention and pleasantness levels (the latter only in case of a tactile condition).

EEG data recording

EEG data were recorded using a high-density 128-channel Hydrocel Geodesic Sensor Net (Electrical Geodesic Inc., EGI, Eugene, OR, USA) referenced to the vertex.[48] The EEG signal was amplified with an EGI NetAmps 400 amplifier, digitized at a 1000 Hz sampling rate. No filters were applied during signal recording. Electrode impedances were kept below 50 kΩ throughout the experimental procedure.

EEG pre-processing and analytic strategy

The native Netstation v.5.2.0.2. (EGI) software was used to perform the filtering (band-pass filter of 1–100 Hz, and notch filter at 50 Hz to remove power line noise) and epoching of the raw data. The data for each of the four experimental conditions (B, NoT, DT, AT) were epoched between −200 ms before to 19800 ms after the onset of the first heat stimulus to include the whole of each train of 6 heat stimuli (resulting in 10 'trains' for each participant) and some time beyond the end of the stimulus train. Peaks of the pain of each stimulus would be at 1.5 s, 4.5 s, 7.5 s, 10.5 s, 13.5 s, 16.5 s, with the final offset of pain stimulus at 18 s.

The epoched data were then imported into EEGLAB v14.1.2[49] running on Matlab v.2018b for the remaining pre-processing steps. Firstly, data were down-sampled to 250 Hz and visually inspected to remove sections impacted by system artifacts (e.g. calibration processes). The EEGLAB tools were used to remove bad channels and run ICA; the ICLabel plugin[50] was applied to label components and those flagged as over 90% likely to be attributed to EOG and muscle-related artifacts were removed.[51] Missing channels were then interpolated and re-referenced to the average of all channels.

The average event-related potential (ERPs) amplitudes and Event-Related Spectral Perturbation (ERSP) were derived for each participant for each condition ("NoT", "DT", "AT", "B"). The analyses comprised comparisons across conditions in ERP amplitudes for central/temporal electrodes (Cz and T3). Analyses of ERSP (changes in power along the stimulus train) were expanded to centre on fronto-central FCz, midline Cz and Pz and parietal T3 (the contralateral side to stimulation) and were computed for each channel using EEGLAB toolbox[52] with cycles set to [3, 0.8], for 50 log-spaced frequencies from a minimum of 3 Hz. Spectral techniques such as event-related spectral perturbation (ERSP) have been used over the past 20 years to overcome the limits of the classical ERP model.[52] Focus was placed on frequencies in the delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–35 Hz) and gamma (35–80 Hz) bands.

Statistical analysis

Ratings recorded after each train of stimuli were averaged together for each condition and participant. Given the variability between participants, a check of the outliers was carried out. Out of 144 values, 15 values were identified as outliers (>1.5-times the SD from the group's mean) and replaced with the median score for the relative condition.[53,54] Data were checked for sphericity with Mauchly's test ($W = 0.87$, $p = 0.44$) and all pain data were normally distributed according to the Shapiro-Wilk test (all ps > 0.05). Only the Baseline condition was not normally distributed ($W = 0.49$, $p < 0.001$). However, the F-test has proven to be robust even to great departures from normality.[55] For pain thresholds one-way repeated-measures ANOVAs with the factor "Condition" having 4 levels and Bonferroni-corrected post-hoc tests were used to disclose possible differences among conditions. A non-parametric Friedman ANOVA was run on subjective ratings of attention with the factor "Condition" having 4 levels, while differences in the pleasantness ratings were calculated via a Wilcoxon signed-rank test since those ratings could only be collected in relation to the DT and AT condition.

In relation to the EEG, for both ERPs and ERSPs, the exploratory strategy was to first examine the statistical significance, using automatically randomised permutation calculations, for a one-way ANOVA across all the conditions. No corrections for multiple comparisons were applied at this first stage of exploratory analyses. FDR correction[56,57] was applied in all the planned paired comparisons between: "B" vs "NoT"; "NoT" vs "AT"; "NoT" vs "DT"; "AT" vs "DT". For each Fig., the bottom panel displays statistically significant differences at the alpha level of.05.

Results

All results were calculated with the statistical software JASP.[58] Means and standard deviations related to behavioural results are reported in Table 1, with a graphical representation in Fig. 1. Fig. 2 depicts the grand averages of the pain ratings across the ten trains per each one of the six stimuli and conditions.

Pain ratings

The one-way repeated-measures ANOVA on the pain thresholds disclosed an effect of the factor "Condition" $F(3,105) = 124.5$, $p < 0.001$, $\eta p2 = 0.78$), revealing that the pain sensation did variate across conditions. Bonferroni-corrected post-hoc tests showed that, as expected, all pain conditions felt pain compared with the Baseline condition (all $p_s < 0.001$). Among those where painful stimuli were delivered, only the "AT" condition had significantly lower pain ratings, compared with both the "NoT" ($p = 0.023$) and the "DT" condition ($p = 0.021$). During the "DT" condition there was no significant reduction of pain sensation compared with no touch ($p > 0.05$). Therefore, only "AT" was able to reduce TSSP, confirming our previous finding.[16]

Attention ratings

Results indicated that ratings differed significantly across conditions ($\chi2(3) = 12.39$, $p = 0.006$). Post-hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.0083$. Not surprisingly, there were significant differences between the Baseline and the other conditions ("NoT": $Z = -3.13$, $p = 0.002$; "DT": $Z = -2.87$, $p < 0.004$). Yet, after applying the correction, the attention during the Baseline was not significantly different compared with the "AT" condition ($Z = -2.60$, $p < 0.009$). "NoT" and "DT" did not differ in terms of attention ($Z = 1.00$, $p = 0.32$), nor did they compare with "AT" ("NoT": $Z = -1.69$, $p = 0.091$; "DT": $Z = -0.19$, $p = 0.85$).

Pleasantness ratings

Results indicated that ratings differed between the two conditions receiving the concomitant tactile stimulation, with the stimulation characterizing the "AT" condition being perceived as significantly more pleasant than the tactile stroking received during the "DT" condition ($Z = -4.16$, $p < 0.001$).

EEG results

Event related potentials (ERPs)

ERPs are positive or negative voltage deflections seen in the averages of EEG epochs time-locked to a class of repeated stimulus or response events.[59] At both electrodes, the baseline (no pain and no touch) showed a 'steady' signal across the time of the stimulus train. Pain (no touch) elicited changes from the baseline in synchrony with the stimulus intensity such that amplitudes at Cz were more negative with pain, whereas for T3, amplitudes were more positive with pain compared to baseline. When touch is added to pain (both fast and slow touch), the pattern is reversed, such that touch appears to 'return' average amplitudes back towards those of the baseline with no pain. Thus, the general pattern appears that the effect of pain on ERP is reversed by the addition of touch (Fig. 3 upper panel). Although the conditions did differ in the omnibus comparison, these did not stand up to the FDR correction for any of the planned paired comparisons.

The corresponding topoplots (Fig. 3 lower panel) indicate that there were differences in the left parietal and midline regions, between "B" vs "NoT" conditions and "NoT" vs "AT" and "DT" conditions as might be expected. However, these did not survive FDR correction for comparisons of topoplots between pairs of conditions.

Table 1
Average means (and SDs) of pain, attention and pleasantness ratings.

Condition	Pain ratings (CoVAS)	Attention ratings	Plesantness ratings
B	0.9 (1.7)	5.73 (3.2)	—
NoT	43.1 (17.2)	7.41 (2.03)	—
DT	42.9 (17.8)	7.18 (1.9)	3.1 (2.7)
AT	36.1 (16.9)	7.06 (1.8)	4.7 (2.6)

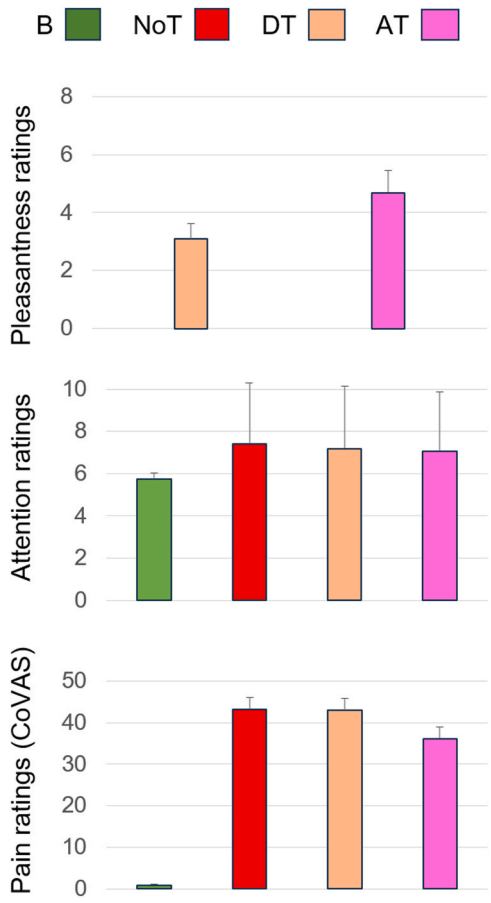

Fig. 1. Grand averages (histograms) and standard errors (error bars) of pleasantness, attention and pain ratings in each condition [Baseline ("B") in green, no touch ("NoT") in red, discriminative touch ("DT") in light brown and affective touch ("AT") in fuchsia].

Event-related spectral perturbation (ERSP)

ERSPs are a measure of a mean change in spectral power compared to baseline that are time-locked and induced by a stimulus.[60] The average ERSP across participants for each condition at each electrode location, along with the areas of statistically significant differences, are shown in Fig. 4. The analysis of ERSP indicated that when pain alone was induced ("NoT"), power increased in frequencies mainly associated with the alpha band, and that this was statistically significant at FCz. At T3, the power was decreased on application of pain, especially so in the delta and theta bands. The boxes in Fig. 4 indicate the areas of statistical significance (with FDR correction) for each of the planned paired comparisons.

There did not appear to be an effect to the pain response when "DT" was applied, however, when "AT" was applied, a reduction in power (compared to "NoT") was observed in delta, theta, beta and gamma bands at Cz and Pz. The difference between "AT" vs "DT" was also mainly

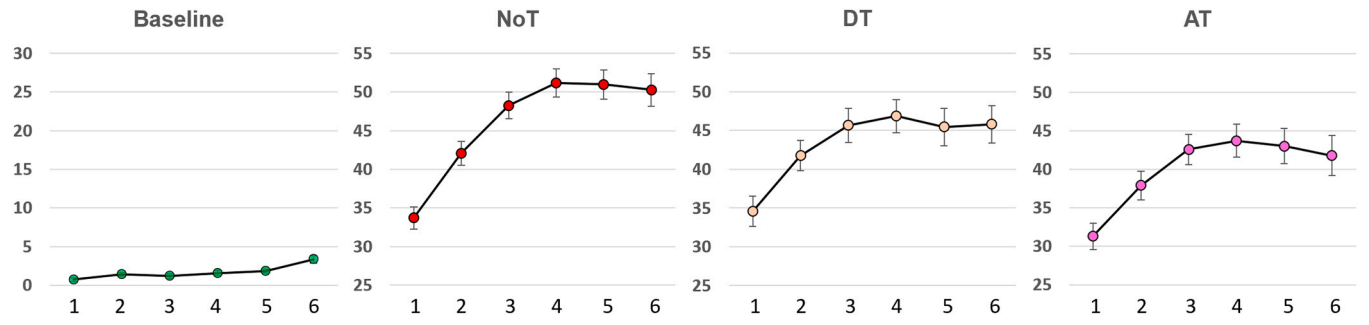

Fig. 2. Grand averages (circles) and standard errors (error bars) of pain ratings across the ten stimulation trains per each one of the six stimuli and per each condition.

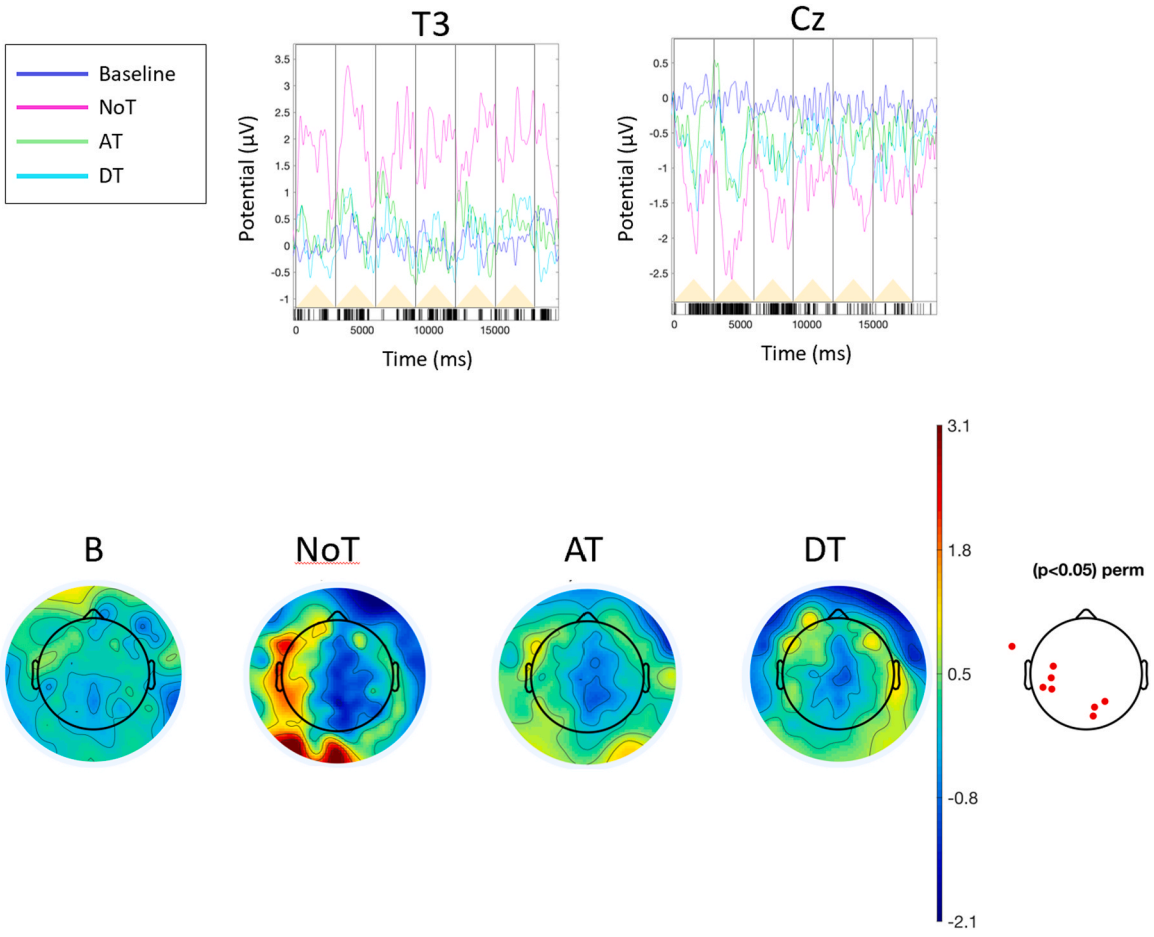

Fig. 3. Upper panel: Grand-averaged ERP for each condition ("B": Dark Blue; "NoT": Pink; "AT": Green; "DT": Light Blue) along entire train of 6 heat (pain) stimuli to 18 s. Each individual stimulus lasts 3 s (time window of each heat stimulus indicated by boxes; triangles indicate the stimulus intensity, with peaks at 1.5 s; 4.5 s; 7.4 s; 10.5 s; 13.5 s; 16.5 s); high pass filtered at 10 Hz for visualisation only. Lower panel: Corresponding topoplot across 18 s train.

observed at Cz and Pz, with "AT" lower in power than "DT", however, only the difference at Pz in the beta band was statistically significant upon testing the paired comparisons between these two conditions. This provides an indication of a possible distinct marker of type of touch ("AT" vs "DT") within the beta band, centred at about 26 Hz at Pz. The topoplots in Fig. 5 indicate that this is located along the posterior midline.

Correlational analysis

To reveal any possible connection between the pain ratings and the subjective ratings of attention and pleasantness, a correlational analysis was run. Spearman's rho was considered to check any possible correlation between the pain obtained during each condition and the other subjective ratings. No significant correlation was disclosed (all $p_s > 0.05$). It should be noted however that, to our knowledge, no correlation has ever been reported between AT-modulated pain scores and touch pleasantness ratings in other acute pain studies with AT (e.g., [38,61–64]).

Correlational analyses were also run between the mean spectral power in the different bands at central (FCz, Cz and Pz) and contralateral (T3) locations and the pain ratings, but no significant correlations were found (all $p_s > 0.05$).

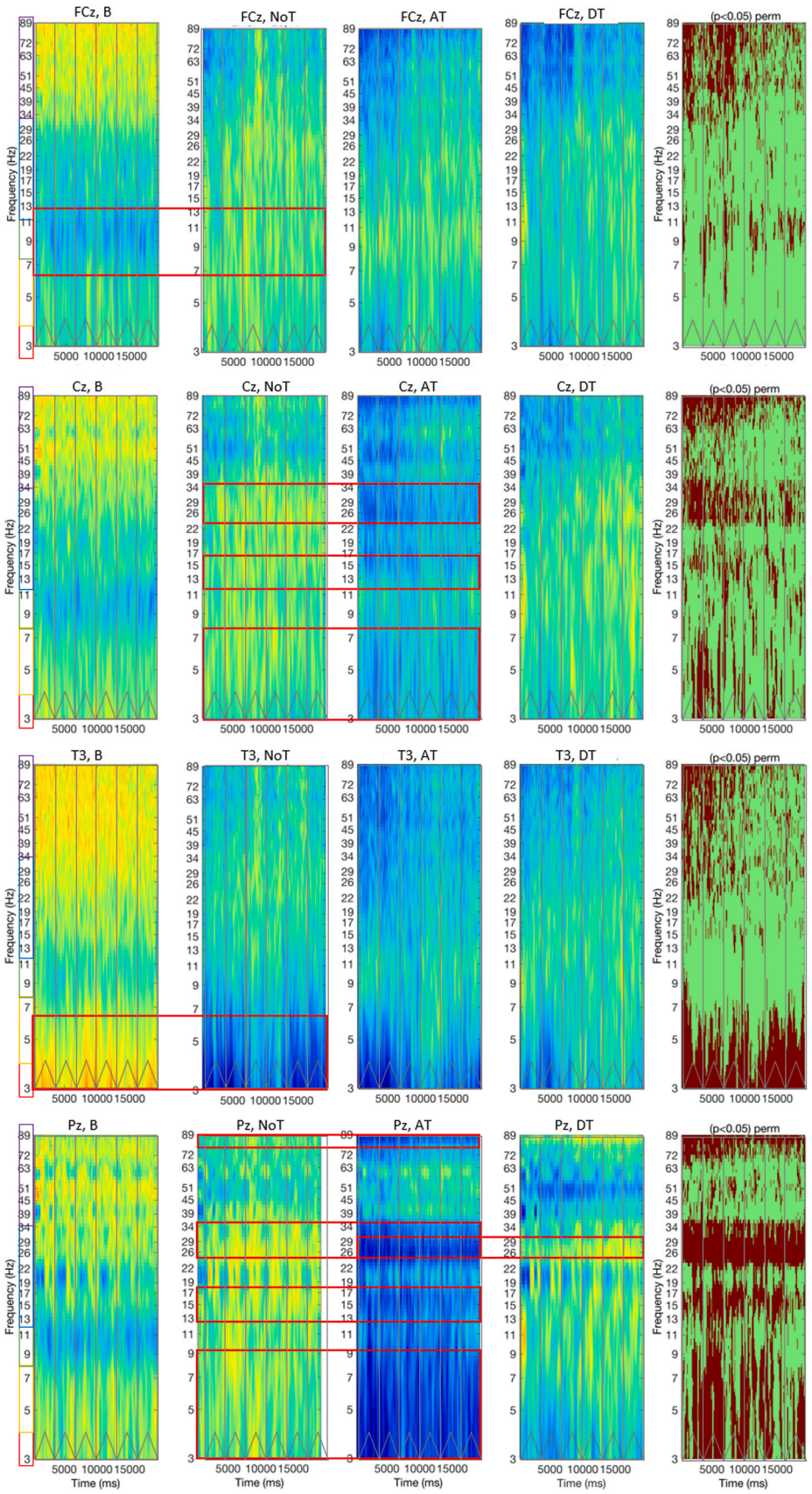

Fig. 4. ERSP for each condition. Rightmost panel shows the areas of statistically significant differences across conditions at less than $p = 0.05$. The red boxes indicate where the paired comparisons between conditions showed statistical significance surviving FDR correction.

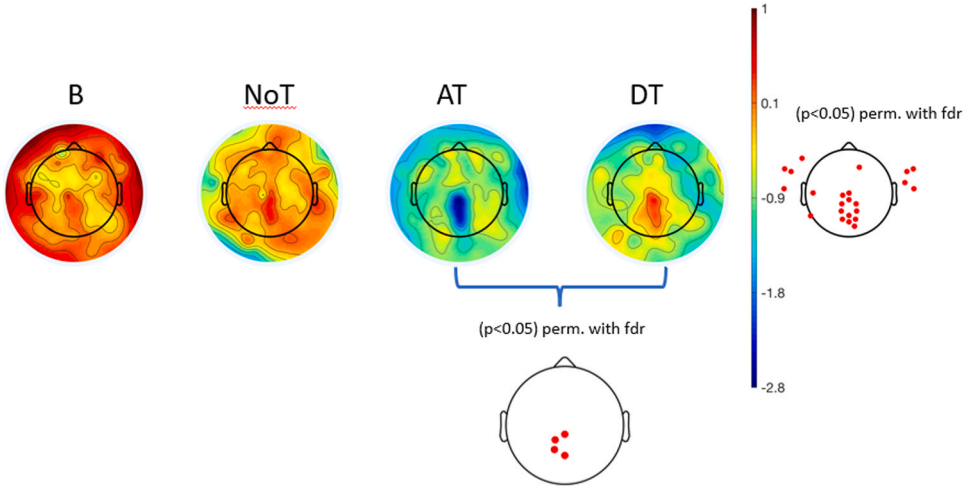

Fig. 5. Topoplots for each condition within the beta band. Rightmost panel shows the areas of statistically significant differences across conditions at less than p = 0.05. The comparison between "AT" and "DT" conditions shows statistically significant differences along midline posterior electrodes as indicated in the electrode map below those conditions.

Discussion

Starting from the behavioural results, in line with the outcomes of our previous study,[16] we found that AT was the only tactile modality to be perceived as more pleasant and able to significantly decrease the pain sensation derived by a TSSP protocol. The socially-relevant and pleasant tactile experience which classically relies upon the activation of CT fibers is not new to bring about pain relief. For example, it is known that AT is able to induce a robust reduction of experimentally-induced acute pain too.[36,38,61–63,65] Recently, another work employing a TSSP protocol has shown that CT-optimal touch can effectively reduce TSSP not only when applied on the ipsilateral side of pain induction, but also when applied on the contralateral side.[66] Here, we also found that the DT condition did not produce any substantial pain reduction. Although this may be counter-intuitive given that a tactile stimulation can be associated with pain relief,[67] this result is in line with our previous AT-TSSP study where DT did not show any analgesic properties.[16] Evidence in favour that not all tactile stimulation has pain relieving effects comes also from a recent study, showing that when AT precedes pressure pain the pain felt is lower, but when a tapping gesture precedes the pain, the pain is rated as even more intense.[63]

While the analgesic properties of AT seem to be quite robust, little is still known about its neural underpinnings. More importantly, at present, very few studies have investigated the brain responses associated with TSSP, and there are none related to AT-driven pain modulation during TSSP. ERSP provides a mean change in spectral power from baseline and can be viewed as a generalization of ERD/ERS.[52,60] On this, our results provide various insights. Firstly, our ERSP analysis showed a delta and theta band decrease over T3 during TSSP alone ("NoT") compared to the non-painful stimulation ("B"). Along with variations in other spectral bands, a reduction of fronto-temporal theta activity can be reported during the delivery of strong somatosensory (not pain-specific) stimulation.[68] Hence, a change in lower frequencies over temporal electrodes may not be the best candidate as a possible EEG cortical marker of TSSP. Yet, this is still premature to say since only two studies have, so far, investigated the neuro-electrophysiological correlates of temporal summation of pain,[40,69] and only one, besides the current work, has delved into its time-frequency domain.[69]

Secondly, the analysis of the ERSP also indicated that TSSP alone, compared to the non-painful baseline, was accompanied by an increase in the alpha range at a frontal-central region. Event-related synchronization (ERS) in the alpha band has been hypothesized to reflect cortical deactivation or inhibition,[70] but while alpha ERD/ERS over sensory and affective matrices may reflect some kind of sensory/affective and also cognitive modulatory effects,[71] frontal alpha patterns are less clearly defined. Zhang and colleagues recorded, along with a global desynchronization in the lower frequency bands (1–13 Hz) in the frontal, left parietal, right parietal and occipital regions also a local increase in alpha power in the frontal area during sustained thermal stimulation.[72] Alpha ERD/ERS over prefrontal or parietal regions may also reflect cognitive modulations due to anticipation/expectation.[71,73] In a study conducted on chronic pain patients with spinal cord injury (SCI) it was reported an association between an increase in the alpha activity over frontal electrodes and an increased pain sensation.[74] The authors of this study suggested that the increase in frontal alpha may reflect an attempt to engage in processes which lead to pain suppression, which would be consistent with the findings from tDCS studies, aiming at increasing activity in the prefrontal motor cortex to facilitate pain suppression.[75]

Thirdly, adding AT to TSSP led to a reduction in power of delta, theta, beta and gamma frequencies at Cz and Pz compared to the pain alone condition. More specifically, while at Cz only lower frequencies and upper beta were involved by such neuronal oscillatory suppression, at a more posterior central electrode (Pz) all frequency bands (i.e. lower frequencies including lower alpha, upper beta and higher gamma) were involved in the power decrease. This novel observation may be attributable to the specificity of the pain stimulation protocol (TSSP) in conjunction with the modulatory agent (AT) which have been the objects of the current study. In fact, although another study also showed activity changes at multiple frequencies for both pain- and touch-related neuronal oscillations, their study focused on discriminating these neural signatures of pain and touch perception and encoding stimulus intensity. Theta and gamma activity increased in response to both pain and touch, while a stronger alpha reduction was reported during touch.[76] Reduced low- and high-frequency brain oscillations in parietal areas have been recorded during a state of “thoughtless emptiness” reached by experienced meditators.[77] Such a state is supposed to express a reduction of mental processing and relaxation.[77] A reduced parietal alpha and beta activity has been also recorded during the initial resting period after a breathing exercise which induces a state of calmness.[78] Hence, compared to pain alone, the brain response associated with AT may reveal a lower propensity to engage in pain processing mechanisms and a higher relaxation state during the pleasant tactile experience, which is not induced when the concomitant tactile stimulation is not particularly pleasant (i.e. during DT).

Fourthly, we found a significant reduction of beta power at Pz during AT, not only compared to during pain alone, but also and more

specifically compared to during the other tactile stimulation. Aftanas and coworkers reported a decreased beta power in relation to emotional stimuli of different valence (happiness and sadness), in fronto-central and occipital areas.[79] Interestingly, von Mohr and collaborators demonstrated how the neuronal oscillations linked to affective touch, in comparison with non-affective touch, not only exhibit a frontal (prefrontal and frontal), temporal and posterior (parietal, occipital) reduction of theta activity, but it is also characterized by a reduction of beta activity which is specific to the parietal area.[64] Considering the due differences between ours and von Mohr's study (for ex. in the present work both types of tactile stimulations were coupled with an underlying painful stimulation), and keeping in mind that the only significant change reported during AT vs. DT was the beta reduction at Pz, we speculate that the parietal drop in the beta range may be a specific brain response associated with AT, present also during TSSP. In support of this idea may come the other results from von Mohr's study which showed how non-affective touch yielded oscillatory changes in the alpha and beta ranges at different scalp sites compared to a resting condition, but not a parietal beta reduction.[64] The presence of concomitant pain and touch in both tactile conditions of our study may lead to the 'cancellation' of other frequency modulations in the AT-DT comparison, leaving the marked parietal beta reduction to stand out specifically for the pleasant, affective tactile stimulation. After all, although beta oscillations have been shown to be altered by some pain conditions/states (for ex.[80–82]) and considering that, depending on the experimental design and pain type considered, the frequency bands involved can sensibly vary among studies,[83] there is an indication that the beta band would not specifically contribute to the coding of pain and that it would exhibit an on/off behaviour during tactile stimulations.[76] Rather, parietal-beta may reflect emotional regulatory mechanisms linked to the affective representation of tactile stimuli[64] or an 'intersensory attention' process, diverting attention towards a tactile stimulus while disregarding one in another sensory modality.[84] This said, it should also be considered that there were no significant differences in terms of attentional levels among the experimental conditions. Hence, if the parietal beta modulation is linked to intersensory attentional processes, these are likely to be unconscious mechanisms and therefore cannot be measured through subjective reports. This also means that greater pain suppression experienced by the participants during the AT cannot be directly attributable to mere attentional variables, but rather to other factors, some of which would call into play the activation of C-tactile fibres. Indeed, CT fibres must be intact to be able to express their influence on pain, as testified by patients with small fibre neuropathy who do not report any benefits from a CT fibres stimulation.[38] It should be considered however, that despite being a spinal phenomenon, TSSP can be modulated by supraspinal attentional mechanisms[85] and a recent TSSP study showed lower levels of attention during CT fibres stimulation,[86] so a contribution of distraction to the pain-relieving effects of AT may not be completely excluded.

Finally, it should be noted that female subjects usually report greater TSP responses than male,[69] however, our preliminary analysis failed to show such sex-driven difference.

To conclude, with the current study we not only confirmed the efficacy of AT in dampening pain elicited by a TSSP protocol, but we also provided an investigation into the neural underpinnings of both TSSP and AT-driven TSSP modulation. In particular, the specific parietal beta reduction found during AT compared to either TSSP or TSSP with DT, may shed light on how the brain conjugates pain management during a repeated painful stimulation with an emotional regulatory mechanism related to the affective qualia of CT fibres activation. Future investigations are warranted to reveal whether the same posterior neural pattern shows during TSSP protocols with AT stimulation in patients with chronic pain (for instance those with fibromyalgia) or if such neural pattern is absent/altered. Brain stimulation studies could further explore if the central parietal area can be a target to alleviate chronic pain in those with central sensitization problems.

Author contributions

MM conceptualized the experiment. FF and MM ran the experiment. EW and MM did the analyses and the Fig.s. All authors contributed to the writing of the manuscript, from its draft until its final version.

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Disclosures

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Data Availability

A copy of the original data will be available upon request.

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