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The effects of tapentadol and oxycodone on central processing of tonic pain

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HIGHLIGHTS

- In a population of healthy male men, oxycodone and tapentadol reduced pain perception.
- Spectral analysis and source localization showed differences in the central processing of tonic pain between oxycodone and tapentadol.
- Different mechanisms of action were involved, but oxycodone affected cortical structures more than tapentadol.

ABSTRACT

Objective: The present study investigated differences between opioids to experimental tonic pain in healthy men.
Methods: Twenty-one males participated in this cross-over-trial. Interventions twice daily were oxycodone (10 mg), tapentadol (50 mg) and placebo for 14 days. Tonic pain was induced on day 1, 4 and 14 by immersing the hand in 2 °C water for 120 s. Electroencephalography was recorded during test pain at baseline and after 14 days. Spectral analysis and source localization were investigated in predefined frequency bands.
Results: A decreased perception of pain on day 4 persisted throughout the 14 days compared to baseline ($p < 0.006$). Oxycodone decreased the electroencephalography spectral power in the delta and theta bands and increased power in the alpha1, alpha2 and beta1 bands ($p < 0.03$). Tapentadol increased spectral power in the alpha1 band ($p < 0.001$). Source localization revealed that oxycodone decreased activity of the temporal and limbic region in the delta band, and frontal lobe in the alpha2 and beta1 bands, whereas tapentadol decreased alpha1 band activity in the temporal lobe compared to placebo.
Conclusion: Oxycodone and tapentadol reduced pain perception and changed the central processing of tonic pain.
Significance: Different mechanisms of action were involved, where oxycodone affected cortical structures more than tapentadol.
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1. Introduction

Chronic pain is one of the most frequent symptoms in a variety of diseases, affecting approximately 20% of the Western world (Dahlhamer et al., 2016; Fayaz et al., 2016; Larsson et al., 2017). Opioids may be used as treatment of moderate to severe pain when simple analgesics fail (Staahl et al., 2009). In the clinical setting, morphine has been widely used, but other strong opioids include e.g. oxycodone, buprenorphine, hydromorphone, methadone, alfentanil, fentanyl and tapentadol. These drugs are predominantly mu-opioid receptor agonists (Drewes et al., 2013). A downside of most strong opioids are side effects such as nausea, sedation, vomiting and constipation (Drewes et al., 2013). Tapentadol exerts its analgesic effect by combining a mu-opioid receptor agonistic effect like conventional opioids combined with noradrenalin re-uptake inhibition with a synergistic mechanistic analgesic effect (Drewes

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et al., 2013; Langford et al., 2016). Knowledge regarding the different treatment-related mechanisms and their influence on the pain processing in the central nervous system in humans is limited, as most studies have evaluated the treatment effect in either animal studies or on self-reported data (Malver et al., 2014). These confounding factors can, to some extent, be avoided by using standardized experimental pain models in healthy subjects (Drewes et al., 2013; Malver et al., 2014). Different methods have been introduced to visualize changes in the central nervous system during treatment with analgesics such as electroencephalography (EEG), magnetoencephalography and magnetic resonance imaging (Saab, 2013). Recordings of spontaneous electrical brain activity using EEG in combination with a tonic pain stimulation, either hot or cold, have previously been used to demonstrate changes in the central nervous system, and it has proven to be reliable between days (Gram et al., 2015). Gram et al. found an association between objective cortical activity and subjective pain perception (Gram et al., 2015). The underlying source generators of these differences within the brain can be analyzed using standardized Low Resolution Electromagnetic Tomography (sLORETA) (Pascual-Marqui et al., 2011, 1994). Previously, the effects on central processing of tonic pain have been investigated comparing five days treatment with opioid (oxycodone) and an antidepressant (venlafaxine) to placebo using both spectral analysis and sLORETA (Lelic et al., 2017). The study showed that both drugs induced changes in the topographical representation of EEG compared to placebo, but without major differences (Lelic et al., 2017). One reason could be that the analgesic effects of noradrenalin re-uptake inhibition normally take weeks to manifest in clinical practice (Aiyer et al., 2017; Joshi, 2018). In this study, the effects of two-weeks treatment with tapentadol and oxycodone on central processing of tonic pain were investigated in healthy subjects using EEG. We hypothesized that tapentadol and oxycodone in equipotent doses would exert similar effect on pain perception during tonic pain stimulation, however through different centrally acting mechanisms. The aim was to investigate differences in perceived pain and central processing of tonic pain between oxycodone, tapentadol and placebo on 1) spectral EEG analysis and 2) brain source generators.

2. Methods

The study was a randomized, double-blinded, placebo-controlled, cross-over study with three arms: Tapentadol, oxycodone and placebo. Each study period lasted for 14 days with a minimum of 7 days washout period between study periods. Ethical approval was granted by Region Nordjylland Denmark (N-20170009), all participants gave written informed consent before entering the study. The study was registered in the public database (EUDRACT, ref 2017–000141-52). Data in this present study is a subset of a larger study with the main objectives to investigate the effect of tapentadol and oxycodone on the central, the autonomic and the enteric nervous systems. Other data based on this trial are available in (Mark et al., 2021a, 2021b).

Included subjects were randomized to the order of treatment (randomization.org). Mirror randomization was performed in case of participant drop out. The research was carried out at the research facilities of Mech-Sense, Department of Gastroenterology & Hepatology, Aalborg University Hospital, Aalborg, Denmark.

2.1. Study participants

Twenty-one healthy participants participated in this study. The inclusion criteria were: Male, age 20–45 and of Scandinavian descent. The subjects underwent a clinical examination by a doctor who ensured that they were healthy and opioid naïve. Exclusion criteria were: Known allergy towards pharmaceutical compounds similar to those used in the study, participation in other studies within 3 months prior to the first visit, expected need of medical/-surgical treatment during the course of the study, history of psychiatric illness, history of persistent or recurring pain conditions, nicotine consumption, daily alcohol consumption, personal or family history of substance abuse, use of any medication including herbal as well as any over-the-counter drugs within 48 hours before start of the study period, intake of alcohol within 24 hours before start of the study period, use of prescription medicine, and need to drive motor vehicle within the treatment periods.

2.2. Medications

Tapentadol (extended release 50 mg, Palexia®, Grünenthal GmbH, Aachen, Germany) and an equipotent dosage of oxycodone (extended release 10 mg, OxyContin®, Bard Pharmaceuticals Ltd, Cambridge, United Kingdom), as well as matching placebo tablets were used. Medication was masked to similar resemblance using DBcaps® (red color, size AA, 13.07–14.44 × 9.39 mm, Capsugel®). These are shell capsules of hard gelatin that hides the appearance of the original tablets without affecting the drug release properties of the original tablets (Esseku et al., 2010; Maher et al., 2019). Medication was administered once orally on day 1 (after baseline measurements) and day 14 (in the morning), and twice a day on day 2–13 (morning and evening). In total 26 doses were administered per treatment arm. The medication was handled, packed, and delivered by the Hospital Pharmacy, Central Denmark Region, Denmark who also performed the randomization of treatment order of the study.

2.3. Experimental procedures

A tonic pain stimulus was performed on day 1 (baseline), day 4 and day 14. EEG was recorded during the tonic pain stimulus at day 1 and day 14. An overview of the data recording is visualized in Fig. 1.

2.4. Tonic pain stimulus

The cold pressor test was performed by immersing the left hand in chilled recirculated water (2.0 °C) (Grant; Fischer Scientific, Slangerup, Denmark). The subjects were told to keep their hand in the water for as long as they could endure and maximally up to 120 seconds. They were asked to rate the pain perception on a numeric rating scale (NRS) 120 seconds after submerging the hand into the water. After having rated the pain the subject withdrew their hand from the water. The NRS ranged from 0 to 10, where 0 = no pain, 1 = first sensation of pain, and 10 = maximum imaginable pain (Carlsson, 1983).

2.5. Data recordings

A 61-channel prewired Ag/AgCl surface electrode EEG cap (MEQNordic A/S, Jyllinge, Denmark) was used for EEG recordings. Electrode gel was applied to keep impedance below 5 kΩ. EEG was recorded while subjects had eyes open in continuous mode with a sample rate of 1000 Hz (SynAmp; Neuroscan, El Paso, TX) and stored for offline analysis. An overview of the data analysis flow is visualized in Fig. 1.

2.6. Data preprocessing

Data were preprocessed using MATLAB (R2019b Mathworks, Inc, Natick, MA, USA) and EEGLAB toolbox (version 14.1.2; Schwartz Center for Computational Neuroscience, Institute for

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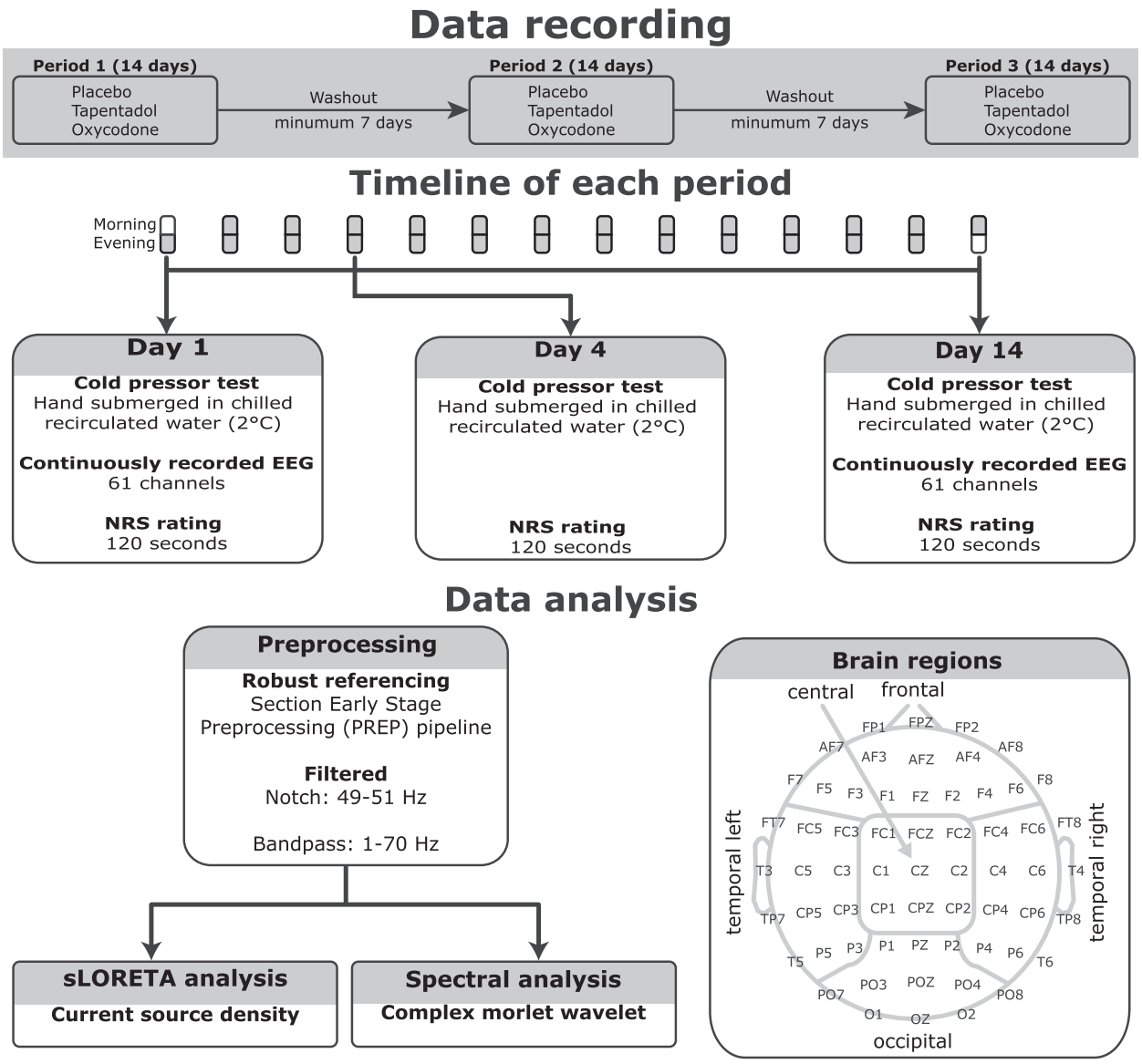

Fig. 1. Data recording at day 1 (baseline), day 4 and after end treatment day 14. Each participant received their treatments in a randomized order. One tablet was taken on day 1 after the baseline measurements and on day 14. The participants received two tablets on day 2–13. Electroencephalography (EEG) was recorded at day 1 and 14 and pain perception using a numeric rating scale (NRS) was recorded at day 1, 4, and 14. The analysis flow including preprocessing and extraction of data for spectral and standardized Low Resolution Electromagnetic Tomography (sLORETA) analysis is described in the data analysis section. The electrodes contained in each brain region used in the spectral analysis are displayed at the lower right.

Neural Computation, University of California, San Diego, CA, USA). Robust referencing was applied using the Section Early Stage Preprocessing (PREP) pipeline (Bigdely-Shamlo et al., 2015). The PREP pipeline is a multi-stage robust referencing design that incorporates the effect of noisy channel-reference interaction. Data were notch filtered between 49 and 51 Hz and bandpass filtered between 1 and 70 Hz. The data were visually inspected, bad channels were interpolated using spherical interpolation (Ferree, 2006; Perrin et al., 1989) and lastly average referenced. Only data in the frequency range 1–32 Hz was included in further analysis due to high amounts of noise persisting after preprocessing in a substantial number of recordings.

2.7. Spectral analysis

Data analysis was performed using a complex Morlet wavelet with a bandwidth of 10 Hz, a center frequency of 1 Hz and a between-scale frequency resolution of 0.5 Hz (Gram et al., 2015; Lelic et al., 2017). Seven frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (12–18 Hz), beta2 (18–24 Hz) and beta3 (24–32 Hz) and five brain regions were extracted (frontal, central, occipital, temporal-left, and -right). The power was normalized for each electrode and described as a fraction of total power across the seven frequency bands (the total amount of power across frequencies summing to 100). The normalized power from each brain region was created by making an aggregated value. This was done by averaging all electrodes in the corresponding brain region resulting in a single power value for each frequency band for each brain region. The locations of the cortical regions and corresponding electrodes are described in Fig. 1.

2.8. Source localization analysis

The sLORETA software package (v20190617) (Pascual-Marqui, 1999; Pascual-Marqui et al., 1994) was used to analyze the cortical

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distribution of current source density. The preprocessed EEG was further processed for optimal sLORETA analysis by downsampling the data to 256 Hz and divided into 60 epochs of 2 seconds. The sLORETA analysis was performed in the frequency domain to localize neuronal activation in the same frequency bands as used in the spectral analysis. For all subjects the average over all epochs was applied. The head model used in sLORETA analysis was based on the Montreal Neurological Institute average MRI brain map (MNI152).

2.9. Statistical analysis

The NRS measures were compared using a repeated measures mixed model with treatment (placebo, oxycodone, tapentadol) and day (1, 4, 14) as factors.

The EEG spectral data were compared using a repeated measures mixed model with treatments (placebo, oxycodone, tapentadol) and cortical regions (frontal, central, occipital, temporal left, and temporal right) as factors. Data were analyzed independently for each frequency band, and post hoc analysis of the brain regions was performed using Bonferroni correction.

The sLORETA algorithm calculates differences in cortical processing between two conditions, based on standardized current density. For sLORETA the statistical analysis was conducted comparing placebo/oxycodone and placebo/tapentadol at both baseline and post treatment recordings for all frequency bands. For each analysis the data was compared at the baseline level to investigate if there were significant differences in baseline measures.

A subgroup analysis was performed by selecting the subjects who had an analgesic effect at day 14 (i.e. a decrease in NRS score at day 14 compared to baseline) in the tonic pain stimulus and perform the EEG spectral data and sLORETA analysis.

All statistical analyses were performed using Stata (StataCore LLC, College Station, TX, version 16.1) and R (R Foundation for Statistical Computing, Vienna, Austria, version 4.0.2). Data are presented as mean ± standard deviations unless otherwise specified. The statistical significance level was set to 0.05 for all analyses.

3. Results

3.1. Study participants

Twenty-three subjects were screened and 22 were included, post inclusion one subject was excluded as he violated the protocol. The demographics for the 21 subjects who completed the study were: age (24.9 ± 2.7 years), height (181.3 ± 6.3 cm), weight (83.2 ± 9.9 kg), body mass index (25.3 ± 2.5 kg/m^2) and 18 of the subjects had right hand as the dominant hand.

3.2. Pain perception

There was an overall decrease in perception of pain in both active treatments on day 4 as compared to baseline (-0.5, p = 0.001). The post hoc analysis revealed a difference in oxycodone (p = 0.006; 95% CI [−1.13, −0.16]) and tapentadol (p = 0.039; 95% CI [−1.12, −0.02]) treatments, but there was no change in the placebo group (p = 1; 95% CI [−0.65, 0.46]). The overall decreased pain perception persisted throughout the 14 days compared to baseline (-0.4, p = 0.006), but post hoc analysis showed that the difference was only significant in the oxycodone arm (p = 0.039; 95% CI [−1.12, −0.02]), with no changes for tapentadol (p = 0.294; 95% CI [−0.93, 0.16]) and placebo (p = 1; 95% CI [−0.69, 0.41]) treatments. Fig. 2 shows the change in perceived pain for the three different interventions compared to their respective baselines.

3.3. Spectral analysis

Baseline recordings: There were no differences at the baseline recordings between the tapentadol and oxycodone arms at any frequency bands. Baseline recordings in the placebo arm differed from the oxycodone arm in the relative wavelet power by 0.32 (p = 0.02) and in the tapentadol arm by 0.51 (p < 0.001) but only in the theta band. The post hoc analysis showed no differences in the individual brain regions.

Changes after treatment: Results for comparisons of data after treatments (day 14) are shown in Table 1 and Fig. 3. The wavelet power in the oxycodone arm differed from placebo in the delta, theta, alpha1, alpha2, and beta1 bands (all p < 0.03). The tapentadol treatment increased compared to placebo in the alpha1 band (p < 0.001). In addition to changes between treatments the wavelet data was also extracted for each brain region and visualized across the frequencies for each brain region and treatment. These are visualized in Fig. 4. Overall the frontal and temporal regions presented the largest amount of power in the lower frequency bands. The active treatments had a lower power compared to placebo.

Changes according to analgesic effect: The overall changes from baseline to post treatment for the oxycodone treatment (n = 10) were: Increases for delta (p = 0.001 95% CI [−3.2, −0.9]), alpha1 (p < 0.001 95% CI [1, 2.1]), alpha2 (p < 0.001 95% CI [0.5, 1.1]), and a decrease in beta3 (p = 0.018 95% CI [−1.2, −0.1]). For tapentadol (n = 9) there were changes in the following bands: An increase for delta (p < 0.001 95% CI [−2.5, −0.8]), and decrease in beta1 (p < 0.001 95% CI [0.3, 0.8]).

3.4. Source localization analysis

Baseline recordings: There were no differences at the baseline recordings for any treatment arm.

Changes after treatment: Recordings during oxycodone differed from placebo in the delta band in the temporal and limbic areas (Brodmann area 20 and 36), and in the alpha 2 and beta 1 bands in the frontal region (Brodmann area 4 and 6). Tapentadol only differed from placebo in the alpha 2 band in the temporal lobe close to insula (Brodmann area 22). Brain regions that demonstrated significant differences between treatments after 14 days are presented in the 61-channel topography is visualized in Fig. 5.

Changes according to analgesic effect: Subgroup analysis showed no differences likely as the sLORETA model needs higher numbers to differentiate changes.

4. Discussion

In the present study we explored the effects of two opioids; oxycodone (mu-opioid receptor agonist) and tapentadol (mu-opioid receptor agonist and noradrenaline reuptake inhibitor) on experimental tonic pain. Changes in EEG spectral indices during tonic pain were demonstrated for both treatments, the inverse modelling showed that oxycodone induced larger changes of the electrical activity in cortical structures, whereas tapentadol mainly affected areas close to the limbic area.

4.1. The analgesic effect of oxycodone and tapentadol

After four days, the subjective pain ratings decreased, this was sustained throughout the study for the oxycodone treatment. The tonic pain model has been shown to be robust in assessing the analgesic effect of analgesics (Staahl et al., 2009). Opioids have previously shown to decrease tonic experimental pain by approximately 14 % compared to placebo (Jones et al., 1988). Our data support these reports as we found decreases of 7–11% for

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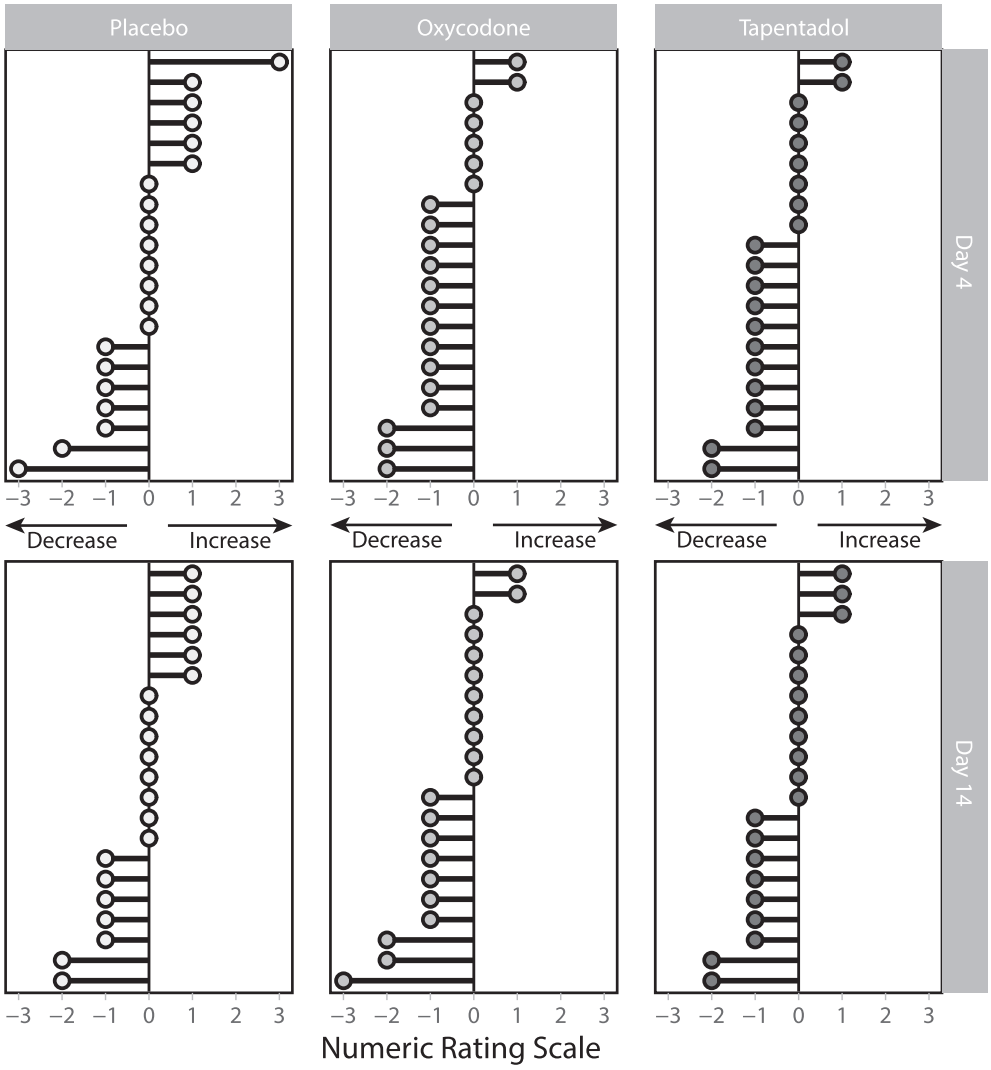

Fig. 2. Pain perception using the numeric rating scale. The change from baseline (0 on the graph) to day 4 and 14 for the three treatment arms are visualized for each study participant. The data is individually ordered from largest negative change (analgesic effect) to largest positive change (higher sensation of pain) for each treatment arm.

oxycodone and 6–9% for tapentadol in comparison to baseline. For comparison placebo had a 4% increase at day 4 and 1% decrease at day 14 compared to baseline.

4.2. The effect of oxycodone and tapentadol on spectral indices

A difference was seen in the baseline recordings of oxycodone and tapentadol compared to placebo in the theta band before correcting for multiple comparison tests. EEG has been shown to be reproducible over time in similar studies (Gram et al., 2015), and is in this case believed to be a type 1 error. The observed change in baseline was persistent in the post intervention for the oxycodone treatment, after the intervention there was a decrease in power as opposed to the positive difference between placebo and oxycodone in the baseline recording. The oxycodone treatment decreased spectral indices in the low frequency bands (delta and theta) and increased spectral indices in the mid-frequency bands (alpha1, alpha2 and beta1). The tapentadol treatment only increased spectral indices in the mid-frequency band (alpha1). The decrease in the lower frequencies during oxycodone treatment has been shown previously (Chang et al., 2002; Ferracuti et al., 1994; Lelic et al., 2017). Furthermore, the study by Lelic et al. found the decrease in the delta band to be correlated with decreases in unpleasantness scores (Lelic et al., 2017). Gram et al. described an increase in the delta band between EEG during resting state and EEG during the cold pressor test (Gram et al., 2015). These findings suggest that the decrease in the delta band for the oxycodone arm could be a result of decreased perception of pain. Theta band activity has also been shown to be correlated to subjective pain scores (Gram et al., 2015).

A similar change to the tapentadol change of the alpha1 frequency was described by Lelic et al. who found an increase in alpha frequencies of a venlafaxine treatment arm (Lelic et al., 2017). Both venlafaxine and tapentadol have a norepinephrine reuptake inhibitor mechanism which could explain the comparable effects. We found an increase in the alpha1 and 2 bands for the oxycodone treatment and only increased alpha1 band activity for the tapentadol treatment compared to placebo. Previous pain studies have shown a decrease in the alpha frequency when submerging the hand in chilled water (Bromm and Lorenz, 1998). The change in alpha frequency is not thought to be pain specific, but more of an adaptive behavior in response to pain (Bromm and Lorenz, 1998). Comparing subjects who had an analgesic effect in the active treatment arms delta activity decreased and beta activity changed (decrease oxycodone and increase tapentadol) compared to baseline, additionally the alpha frequencies increased in the

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Table 1
Spectral analysis of electroencephalography data after 14 days of treatment. All data has average differences, significance and 95% confidence interval displayed. In cases of significance the difference is marked in bold and the post hoc analysis is shown of affected cortical regions.

Frequency band [Hz]	Overall difference, p and 95% CI	Post hoc: Cortical region, p and 95% CI
Oxycodone vs Placebo		
Delta [1–4]	**−2.64 (p < 0.01; [−3.83, −1.46])**	**Occipital: −3.82 (p = 0.020; [−7.30, −0.33])**
Theta [4–8]	**−0.70 (p = 0.03; [−1.35, −0.72])**	
Alpha 1 [8–10]	**1.47 (p < 0.01; [1.1, 1.8])**	**Central: 1.52 (p < 0.001; [0.45, 2.6])** **Frontal: 1.17 (p = 0.024; [0.10, 2.25])** **Occipital: 2.13 (p < 0.001; [1.06, 3.20])** **Temporal L: 1.35 (p = 0.006; [0.28, 2.42])** **Temporal R: 1.19 (p = 0.021; [0.12, 2.26])**
Alpha 2 [10–12]	**0.95 (p < 0.01; [0.62, 1.29])**	**Central: 1.04 (p = 0.032; [0.06, 2.00])** **Occipital: 1.43 (p < 0.001; [0.44, 2.41])**
Beta 1 [12–18]	**0.50 (p = 0.025; [0.07, 0.94])**	
Beta 2 [18–24]	0.35 (p = 0.083; [−0.05, 0.75])	
Beta 3 [24–32]	0.07 (p = 0.802; [−0.49, 0.63])	
Tapentadol vs Placebo		
Delta [1–4	−0.96 (p = 0.110; [−2.15, 0.22])	
Theta [4–8]	−0.57 (p = 0.080; [−1.20, 0.07])	
Alpha 1 [8–10]	**0.62 (p < 0.001; [0.26, 0.98])**	
Alpha 2 [10–12]	0.28 (p = 0.105; [−0.58, 0.61])	
Beta 1 [12–18]	0.34 (p = 0.128; [−0.10, 0.80])	
Beta 2 [18–24]	0.10 (p = 0.610; [−0.29, 0.50])	
Beta 3 [24–32]	0.19 (p = 0.506; [−0.37, 0.75])	

oxycodone arm. The beta band changes have been described in cold pressor tests previously (Chang et al., 2002; Reinert et al., 2000).

4.3. The effect of oxycodone and tapentadol on sLORETA

Brain source activity using sLORETA revealed increases in delta, alpha2 and beta1 band activity confined to the temporal lobe, limbic structures and frontal lobes when comparing oxycodone to placebo. The changes in the alpha2 and beta1 bands are in the left hemisphere, the subjects submerged the left hand in the chilled water. These changes might not relate to the representation of pain but are a part of the adaptive mechanisms, as described in (Bromm and Lorenz, 1998). Tapentadol revealed only minor effects with an increase in the alpha1 band in the temporal lobe compared to placebo. This difference can be due to the dual receptor interactions of tapentadol also affecting the limbic system and lower brainstem spinal levels. Lelic et al. also found similar differences between oxycodone and placebo (Lelic et al., 2017). They also investigated venlafaxine, and did not find any differences compared to placebo (Lelic et al., 2017). The effects of tapentadol compared to oxycodone in the current study are two-fold: 1) A weaker effect of the mu-opioid effect 2) An effect due to the noradrenalin reuptake inhibition relate to the limbic system visual in the difference in insula adjacent areas compared to placebo.

4.4. Scientific and clinical relevance

Our finding support that the dual properties of tapentadol with effects on the opioidergic and noradrenergic systems differ from that of classical opioids on the brains pain processing. This confirms clinical observations such as fewer side effects in equianalgesic dosages (Mark et al., 2021b). Although our results cannot be translated directly to patients with chronic pain, they support that opioid rotation may be beneficial in many cases.

4.5. Limitations

This study was not conducted without limitations. Firstly, data analysis was analyzed from 1 to 32 Hz, excluding information in the higher frequencies (gamma band, 32–70 Hz), these settings were chosen to compare our findings to previous results recorded in the same settings. The current dataset had a low signal to noise

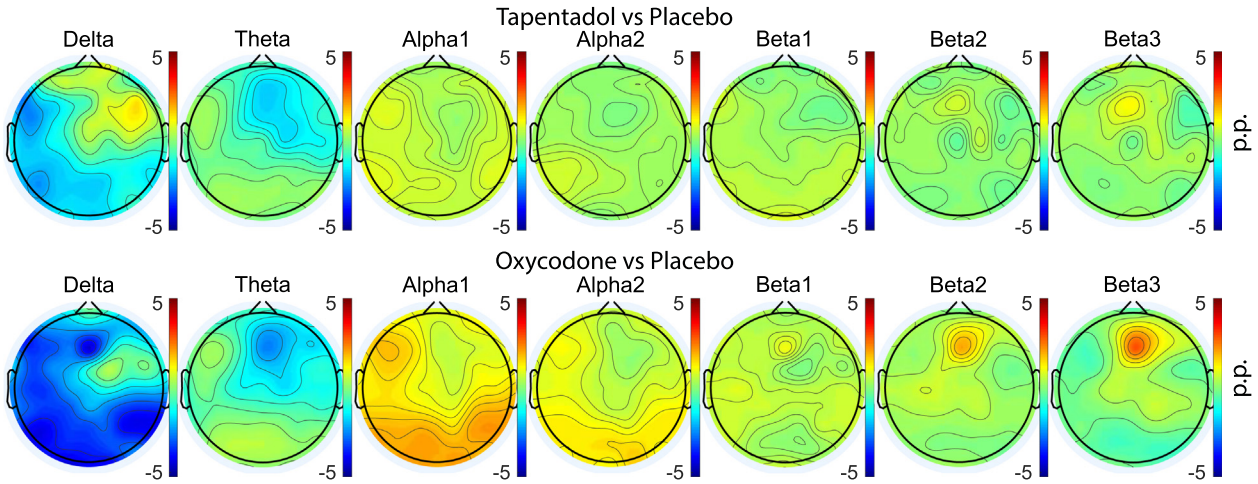

Fig. 3. Spectral topography of the seven frequency bands comparing the percentage point (p.p.) difference in relative power between active treatments and placebo after 14 days of treatment. Changes between treatments are visualized in the heatmaps on the right side of each topography plot. Changes are red if positive (i.e. red color means more activity during active treatment), in blue if negative (i.e. blue color means less activity during active treatment), and green illustrates a difference of approximately 0.

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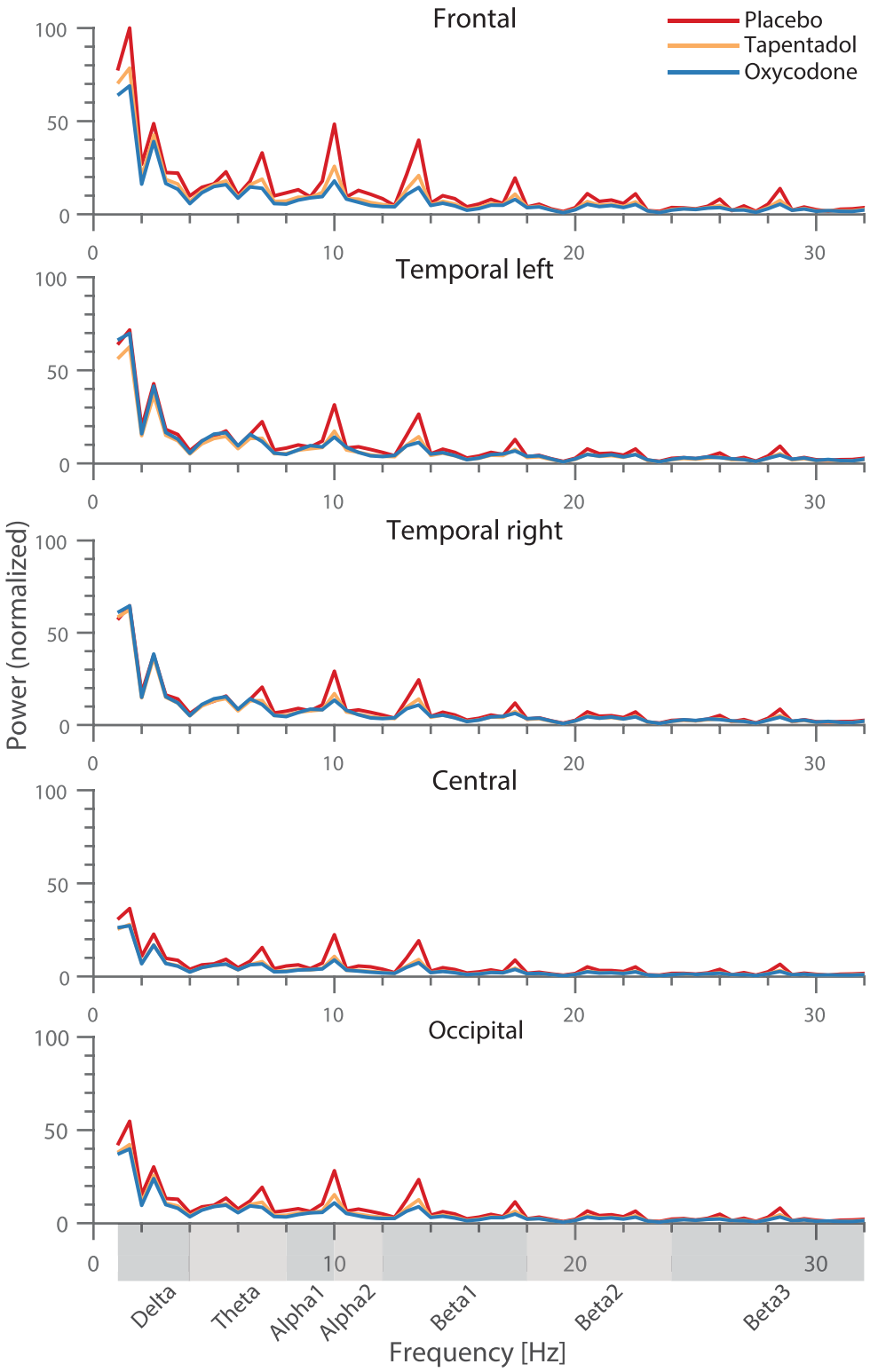

Fig. 4. Visualization of the frequency distribution between 1–32 Hz of power using the Morlet wavelet analysis. The data were divided into five brain regions and normalized to the largest global value across treatments and brain regions. Each brain region contains the three treatments. The frequency bands are displayed in alternating gray shades.

ratio in the gamma band, even after using a robust average reference (Bigdely-Shamlo et al., 2015) along with a Hamming windowed 50 Hz band stop filter. Secondly, the use of EEG brings with it a high temporal resolution, but a poor spatial resolution compared to other brain activity measures (e.g. magnetic resonance imaging). EEG brain source analyses are not precise indicators of brain activity, but rather indicates the center of gravity. They have however been shown to be very accurate (Pascual-Marqui et al., 2011). The strength of these measures is the fact that they provide non-invasive information on brain-processing and can be recorded outside of highly specialized laboratories. However, the use of more information such as individual structural

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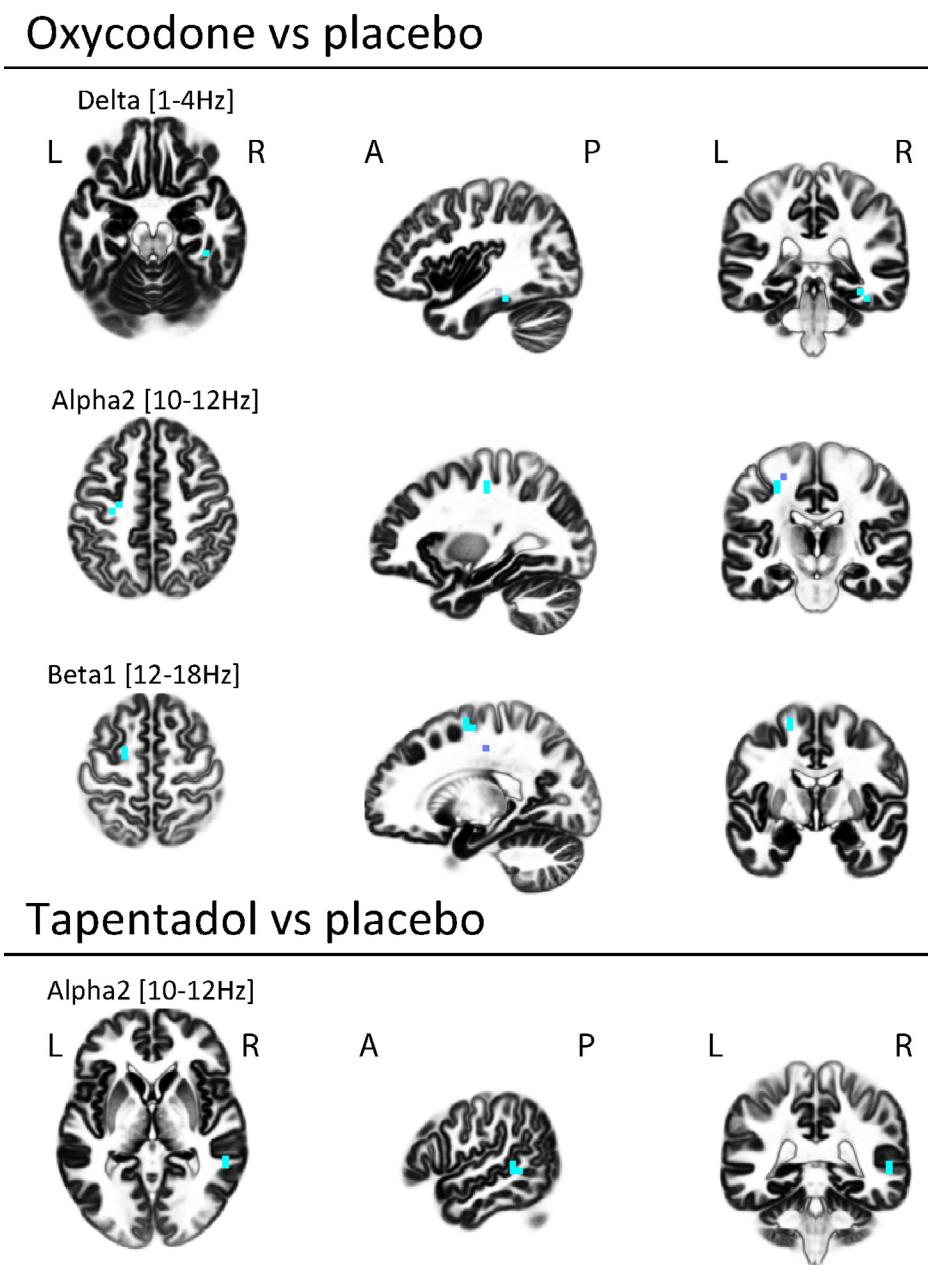

Fig. 5. Change in brain activity using standardized Low Resolution Electromagnetic Tomography inverse modeling between treatments after 14 days. The L and R denote the left and right side of the brain and A and P are the anterior and posterior parts if the brain. The changes highlighted in blue show decreased activity compared to placebo. In the oxycodone arm of the treatment the clusters included: 2 voxels in delta, 3 voxels alpha2 and the 5 voxels in beta1. For the tapentadol arm the observed cluster is 3 voxels.

brain magnetic resonance imaging for sLORETA analysis could add more individual information. This could especially be useful in personalized medicine or in the investigation of treatment effects in chronic pain conditions.

Thirdly no EEG data was recorded on day four of the experiment, this was in part because this study was a larger clinical study with multiple endpoints and it was not feasible to record EEG at all visits. Additionally (Lelic et al., 2017) has shown significant changes in the EEG after oxycodone and venlafaxine (a noradrenaline reuptake inhibitor) after five days of treatment.

Lastly, the experimental pain model was investigated in healthy young men, without taking into account the differences in pain sensitivity and analgesic effect between men and women (Arendt-Nielsen et al., 2004; Bartley and Fillingim, 2013; Fillingim et al., 2009). The interaction of female reproductive hormones and pain both throughout the menstrual cycle and throughout a lifetime is still not well understood (Iacovides et al., 2015). Studies have shown significant differences in pain perception throughout the menstrual cycle (Hellström and Anderberg, 2003) and to avoid this bias to influence the mechanistic effects of the analgesics, only men were included. On the other hand, the rationale of selecting healthy young men was to test these complex experimental models in a homogenous group with well defined nociceptive stimuli. This contrasts a population with chronic pain, or older population multiple comorbidities and adverse effects which often affects the reliability of the outcomes, and masks any mechanistic effects of the medications (Staahl et al., 2009). Future studies should investigate the effects in clinical settings including both male and female participants.

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5. Conclusion

Both oxycodone and tapentadol showed analgesic effects in terms of decreased perceived pain and central processing of experimental tonic pain. For the spectral indices, decreases in the delta and theta bands in the oxycodone arm could be a result of decreased perception of pain. The changes in source localization show a different effect of oxycodone and tapentadol suggesting that oxycodone treatment has a larger cortical effect, and that the pain relieve from tapentadol is derived from the combination of opioid-receptor binding and noradrenalin re-uptake inhibition related to the limbic system. The study replicates preclinical studies demonstrating that different pain control mechanisms are activated by the two opioids in men.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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