Influence of tapentadol and oxycodone on the spinal cord and brain using electrophysiology: a randomized, placebo-controlled trial

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ORIGINAL ARTICLE

Influence of tapentadol and oxycodone on the spinal cord and brain using electrophysiology: a randomized, placebo-controlled trial

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Aims: The aim of this study was to investigate the effects of tapentadol and oxycodone using the nociceptive withdrawal reflex and sensory evoked potentials.

Methods: Twenty-one healthy volunteers completed a cross-over trial with oxycodone (10 mg), tapentadol (50 mg) extended-release tablets, or placebo treatment administered orally BID for 14 days. Electrical stimulations were delivered on the plantar side of the foot to evoke a nociceptive withdrawal reflex at baseline and post-interventions. Electromyography, recorded at tibialis anterior, and electroencephalography were recorded for analysis of: number of reflexes, latencies, and area under the curve of the nociceptive withdrawal reflex as well as latencies, amplitudes and dipole sources of the sensory-evoked potential.

Results: Tapentadol decreased the odds ratio of eliciting nociceptive withdrawal reflex by −0.89 ($P = .001$, 95% confidence interval [CI] −1.46, −0.32), whereas oxycodone increased the latency of the N1 component of the sensory-evoked potential at the vertex by 12.5 ms ($P = .003$, 95% CI 3.35, 21.69). Dipole sources revealed that the anterior cingulate component moved caudally for all three interventions (all $P < .02$), and the insula components moved caudally in both the oxycodone and tapentadol arms (all $P < .03$).

Conclusion: A decrease in the number of nociceptive withdrawal reflex was observed during tapentadol treatment, possibly relating to the noradrenaline reuptake inhibition effects on the spinal cord. Both oxycodone and tapentadol affected cortical measures possible due to μ-opioid receptor agonistic effects evident in the dipole sources, with the strongest effect being mediated by oxycodone. These findings could support the dual effect analgesic mechanisms of tapentadol in humans as previously shown in preclinical studies.

The authors confirm that the PI for this paper is Asbjørn Mohr Drewes.

KEYWORDS
electroencephalogram, electromyography, inverse modelling, nociceptive withdrawal reflex, opioids

1 | INTRODUCTION

Strong opioids are predominantly **μ receptor** agonists.[1] Tapentadol is an opioid analgesic that theoretically employs its analgesic effect by combining moderate μ-opioid receptor agonistic affinity with noradrenaline reuptake inhibition.[2] It has been shown to reduce some of the typical opioid-induced side effects compared to equianalgesic doses of classic opioids[3] and has been investigated preclinically.[3,4] Tapentadol has been found to be an effective and generally well-tolerated treatment in a broad range of chronic pain conditions.[5] However, it is relevant to investigate the central and peripheral mechanisms of tapentadol in order to strengthen the clinical foundation for pain management.

The nociceptive withdrawal reflex (NWR) is a spinal polysynaptic reflex which is the basis for the protective mechanism against possible limb damage.[6,7] The NWR has been used to objectively assess drug-induced effects on nociceptive processing,[7] and has previously been used to determine the analgesic properties of opioids.[7–9] Using a stimulation under the sole of the foot and recording at the tibialis anterior has previously been proven to result in a more tolerable stimulation and good between-session reliability.[10] The reflex threshold, onset latency and area under the rectified curve (AUC) can quantify the NWR[11] and have been shown to change after opioid administration.[12] Additionally, the number of NWRs elicited has recently been used to quantify the difference between people with diabetic peripheral polyneuropathy and healthy controls.[13]

Using the NWR it is possible to investigate the spinal and cortical level of the central nervous system by simultaneously recording electromyography (EMG), and somatosensory evoked potentials (SEPs) using electroencephalography (EEG). On the supraspinal level, SEPs have an excellent temporal resolution and, combined with brain source localization methods, it is possible to estimate the underlying brain sources.[9] Analysis of the supraspinal level of NWR contributes to a deeper understanding of treatments with analgesics.

We performed a randomized, double-blinded, placebo-controlled, cross-over study to investigate the hypothesis that spinal and supraspinal effects would result after 14-day treatment with **oxycodone** and **tapentadol** in healthy subjects.

The aims were to investigate the treatment effects on (1) the spinal level by measuring the number of elicited NWRs, as well as to quantify the NWR using latency and AUC of the EMG response, and (2) the supraspinal level by measuring latencies and amplitudes of the SEPs and inverse modelling of the cortical signals.

What is already know about this subject

- Tapentadol is an opioid analgesic that theoretically employs its analgesic effect by combining moderate μ-opioid receptor agonistic affinity with noradrenaline reuptake inhibition.
- It is relevant to investigate the mechanisms of tapentadol on the central and peripheral nervous systems in order to strengthen the clinical foundation for pain management.
- The nociceptive withdrawal reflex has been used to objectively assess drug-induced effects on nociceptive processing and has previously been used to determine the analgesic properties of opioids.

What this study adds

- Tapentadol affects the number of reflexes observed using the nociceptive withdrawal reflex.
- Both oxycodone and tapentadol affect cortical measures.
- This study replicates preclinical studies suggesting that oxycodone and tapentadol activate different pain control mechanisms and support clinical findings.

2 | METHODS

2.1 | Subjects and ethics

The study was carried out at Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark. Participants gave written, informed consent before participating in the study and were free to withdraw from the study at any time. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20170009) and the Danish Medicines Agency, registered at www.clinicaltrialsregister.eu (EudraCT number: 2017-000141-52), monitored by the Good Clinical Practice unit at Aalborg and Aarhus University Hospitals, Denmark, and conducted according to the Declaration of Helsinki. Data in this present study is a subset of a larger study with the main objectives to investigate the effects of tapentadol and oxycodone on the central, autonomic and enteric nervous systems. Other data based on this trial are available in Refs 14–18.

2.2 | Study design

In total, 21 healthy male subjects completed this randomized, double-blinded, placebo-controlled, cross-over study. A sample size of 20 was calculated based on previous studies using the same experimental models, and so 21 subjects were considered sufficient to reach the goal of this study.[19] Each trial arm lasted 14 days and was administered in a randomized order. To remove potential risks of bias, all subjects were opioid-naïve (have not taken opioid doses for 1 week or more) and could not use any medications (analgesic, herbal or over the counter) within 48 hours before the start of the study as well as for the duration of the study.

A treatment period of 14 days was chosen to ensure adequate treatment since previous studies have indicated that the noradrenaline reuptake inhibitor modulation of tapentadol slowly increases and reaches its maximal effect after 2 weeks.[20] NWR measurements were obtained prior to the first dose and after the last dose. Participants were treated with tapentadol extended-release tablets 50 mg (Palexia; Grunenthal GmbH, Aachen, Germany), oxycodone extended-release tablets 10 mg (OxyContin; Mundipharma A/S, Vedbæk, Denmark), and placebo tablets (Hospital Pharmacy Aarhus, Aarhus University Hospital, Aarhus, Denmark) administered orally BID for 14 days. The subjects were administered tapentadol (50 mg) or oxycodone (10 mg), based on previous clinical studies deeming these to be equipotent.[4] Nomenclature related to drugs and molecular targets conforms to the IUPHAR/BPS Guide.[21] To minimize the risk of addiction, only people who had no previous or current history of abuse or addiction were included, as these factors have shown to result in a frequency of abuse of 0.19% in people with chronic pain.[22] Additionally, all subjects were required to fill out a Subjective Opiate Withdrawal Scale questionnaire 3 days after receiving the last dose in all study periods to monitor whether any degree of dependence was developing. Medication was masked to similar resemblance using DBcaps® (red colour, size AA, 13.07–14.44 × 9.39 mm, Capsugel®), which do not affect the drug release properties of the original tablets.[23,24] A single tablet was ingested on Day 1 after baseline recordings (evening dose) and Day 14 before the post-intervention recording (morning dose). Subjects continued their normal daily lives between recordings. To ensure dosing compliance, the subjects filled in a medication diary on ingestion of each pill. Furthermore, all pill containers were returned and the remaining pills, if any, were accounted for. The "wash-out" period between treatments was at least 1 week. All medication was dispensed by The Hospital Pharmacy Aarhus, Aarhus University Hospital, Aarhus, Denmark. All recordings were performed before first ingestion of medication on Day 1 (baseline) or after the last ingestion of medication on Day 14 (post-intervention). The NWR was elicited by electrical stimulation of the plantar skin (site of innervation of the medial plantar nerve). The cathode was placed at the arch of the sole of the right foot (15 × 15 mm, Neuroline 700; Ambu A/S, Denmark), and the anode was placed on the foot dorsum (50 × 90 mm, Synapse; Ambu A/S, Denmark). The electrical stimulations were delivered by an electrical stimulator (Noxitest IES 230, Aalborg, Denmark) consisting of a constant current burst of five square-wave pulses with 1 ms duration and 5 ms between pulses, which was felt as one single stimulus. A custom-made software program (Center for Sensory-Motor Interaction, Aalborg University, Denmark) was used to manage the electrical stimulations. The perception threshold (PT) and reflex threshold (RT) were identified by manually increasing the stimulus intensity with steps of 1 mA. The PT was reached at the stimulation intensity in mA when the first sensation was felt. The RT was identified using the staircase method described in detail previously.[10] Once the RT was found, the intensity needed to elicit a reflex measured in mA was noted and the subject was asked to rate the pain intensity corresponding to stimulus of the RT using a numeric rating scale (NRS) ranging from 0–10, where 0 = no pain, 1 = first sensation of pain, and 10 = maximum imaginable pain. After the RT was identified and rated, the participant received 18 stimuli at three different stimulus intensities with an inter-stimulus interval of 8–12 s. These stimulations were delivered at low intensity (1.3 × RT), medium intensity (1.6 × RT), and high intensity (2.0 × RT), with six stimuli at each intensity in a randomized order. A visualization of the experimental setup is presented in Figure 1.

2.2.1 | Electromyography

During stimulations, EMG data were obtained from the ipsilateral tibialis anterior muscle. The skin was prepared using sandpaper and alcohol to clean the skin before placing two surface electrodes, where one electrode (15 × 15 mm, Neuroline 700; Ambu A/S, Ballerup, Denmark) was placed on the belly of the tibialis anterior muscle, and one electrode (50 × 90 mm, Synapse; Ambu A/S) the ground electrode, was placed just below the patella. Preprocessing was performed by bandpass filtering the signal between 5 and 500 Hz using a zero-phase digital 12th order Butterworth filter.

2.2.2 | Electroencephalography

EEG data from the scalp were recorded during the NWR. A 62-channel surface electrode EEG cap using the 10–20 system (MEQNordic A/S, Jyllinge, Denmark) was placed on the head, and impedance was kept below 5 kΩ. An electrode located between AFz and Fz was used as the reference electrode. EEG data were recorded in continuous mode with open filters. The sampling rate was 1000 Hz (SynAmp, Neuroscan, El Paso, TX, USA). Recordings were stored offline for further analysis.

2.3 | Data analysis

The EMG and EEG data were analysed in MATLAB (R 2019a Mathworks Inc., Natick, MA, USA).

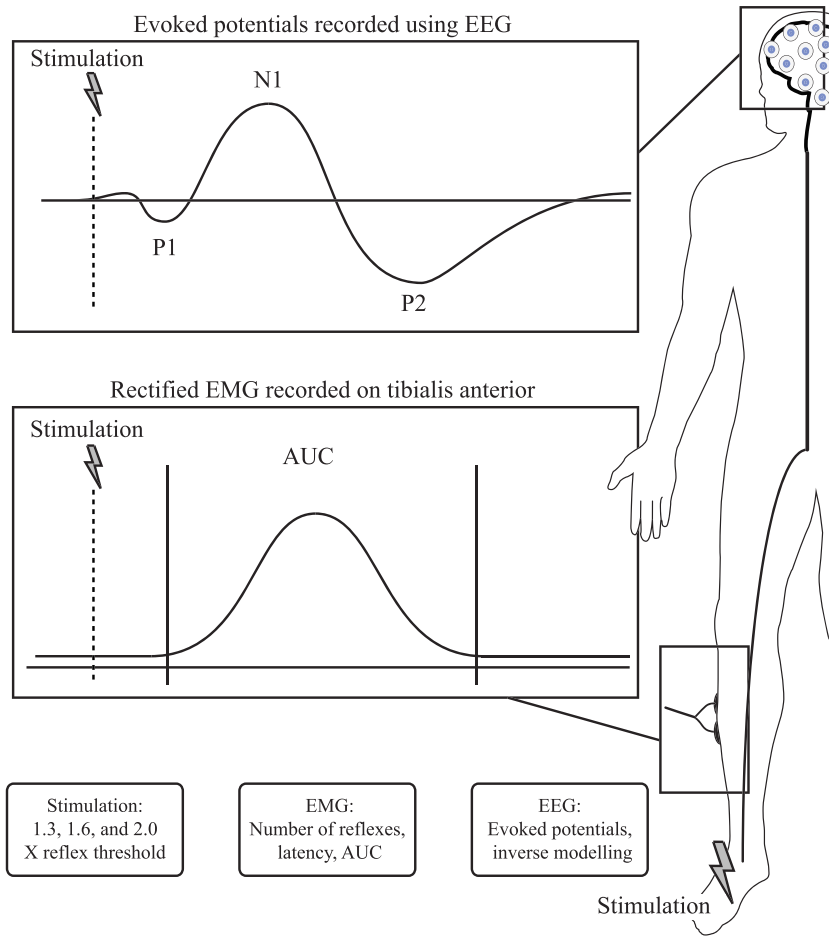

FIGURE 1 Stimulations were provided at the plantar side of the foot. The resulting reflex was recorded using EMG from the anterior tibial muscle. Number of elicited reflexes, latency and area under the curve (AUC) were extracted. Evoked potentials, the first two positive peaks (P1 and P2) and the negative peak (N1) along with inverse modelling using EEG from the cortex were analysed

2.3.1 | Electromyography

The EMG analysis was performed on single sweeps and quantified using the interval peak *z*-score.[25] The z-score was defined by the highest peak in the rectified reflex window minus a pre-stimulus mean divided by the standard deviation (SD) of the same pre-stimulus area. The pre-stimulus window was taken from 100 to 10 ms before the stimulation, while the reflex window was taken from 70 to 160 ms post-stimulus. In all cases, a rectified AUC was calculated in the reflex window. A peak interval *z*-score was set to 6 based on the method described by Herm et al.[26] If any part of the reflex window had a *z*-score above 6, it was interpreted as an elicited NWR. When successfully elicited, the latency was defined at the first point where the rectified EMG trace had a *z*-score above 6.

2.3.2 | Electroencephalography

The EEG preprocessing was performed using MATLAB and EEGLAB toolbox (version 14.1.2; Schwartz Center for Computational Neuroscience, Institute for Neural Computation, University of California, San Diego, CA). The data were bandpass filtered between 1 and 30 Hz. Each recording was manually investigated to identify bad channels and artifacts. These were interpolated using the EEGLAB spherical interpolation method. Lastly, data were epoched from 50 ms before stimulus to 950 ms after the stimulation and averaged for further analysis.

Latencies and peak-to-peak amplitudes of the evoked potentials were assessed. The SEP response at the central electrode (Cz) to electrical stimulation has a triphasic shape, see Figures 1 and 3. The three peaks (P1, N2 and P2) were identified on an average trace for each subject. The Cz electrode was used because of its central location and maximal SEP amplitude due to the electrical stimulation on the foot and its cortical location on the sensory cortex.

Brain source network analysis was performed to study the underlying brain sources generating the SEPs using inverse modelling (BESA research 5.3; MEGIS Software GmbH, Gräfelfing, Germany). The model for the baseline analysis was based on an average of all baseline recordings to get an indication of the location and number of sources. The post-intervention brain source networks were created based on the group-average of each condition. Standardized low-resolution brain electromagnetic tomography sLORETA[27,28] was used to guide the location of the sources for the individual subjects. Once the dipoles were placed in BESA, the model fit was obtained by fixing their locations but allowing their orientations to move freely. The percentage of data that the model could not explain was expressed as the residual variance. The residual variances were sought to be below 10%. All coordinates are reported in Talairach coordinates.[29]

2.4 | Statistical analyses

All data were assessed for normal distribution using Q-Q plots and histograms. In cases of a non-normal distribution, data were log-transformed. For all analyses, the change over time (baseline/post-intervention) was investigated, and the subject was included as a random factor in all analyses.

A multilevel mixed-effects linear regression model with the factors treatment (oxycodone/tapentadol/placebo) and time with subject as a random factor was used to analyse changes from baseline to post-intervention of: the PT and RT of the medial plantar nerve, the subjective pain intensity ratings, the AUC and latency of EMG, the latency and peak-to-peak amplitude of SEPs and location of dipoles of the inverse modelling.

To test the binary outcome of eliciting an NWR (yes/no), a mixed-effects logistic regression model was used against the stimulation intensities (categorical: low, medium and high), treatment (oxycodone/tapentadol/placebo), to investigate the change over time.

A repeated-measures analysis of variance was used with factors treatment (oxycodone/tapentadol/placebo) and time to test if there was a difference in the residual variance of the inverse models between baseline and post-intervention.

Bonferroni post hoc analysis was used to correct for multiple comparisons when analysing the treatment effects when the models showed significant results in time (baseline/post-intervention). All statistical analysis was performed in Stata (StataCore LLC, College Station, TX, version 16.1). *P*-values < 0.05 were considered significant.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021.[30,31]

3 | RESULTS

For this study, 23 subjects were screened, and 22 subjects were included. Twenty-one subjects completed the study (one subject did not comply with the protocol and was excluded). The demographics for the 21 subjects 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). The AUC measure was log-transformed to fulfil a normal distribution. All measures were assessed at the baseline time (all $P > .05$).

Between baseline and post-intervention for each individual intervention, an overall decrease of PT by −0.21 mA ($P = .84$), and increase of RT by 0.07 mA ($P = .9$) were observed; the overall subjective pain scores decreased by −0.16 ($P = .35$).

For the logistic regression, an increased odds ratio of eliciting an NWR was shown with increasing stimulus intensities: medium 2.55 ($P < .001$, 95% CI 1.86, 3.49) and high 2.74 ($P < .001$, 95% CI 1.99, 3.75). The overall odds of observing a reflex decreased over time for the treatments ($P = .001$), and the post hoc analysis showed the change to be in the tapentadol arm −0.89 ($P = .001$, 95% CI −1.46, −0.32). The number of reflexes observed using the interval *z*-score is visualized in Figure 2.

The drug effect on the NWR did not differ from baseline to post-intervention for the latency ($P = .234$) or AUC ($P = .051$). The data are presented in Figure 2.

For the cortical measures of latency at the Cz electrode, the N1 peak was significantly different ($P = .008$), and the post hoc analysis revealed an increase in the oxycodone arm of 12.52 mS ($P = .003$, 95% CI 3.37, 21.69). The P1 and P2 peaks did not differ between baseline and post-intervention (P1: $P = .687$, P2: $P = .732$). For the peak-to-peak amplitudes, neither the P1-N1 ($P = .944$) nor N1-P2 ($P = .915$) amplitudes differed across time. A grand average of the oxycodone trace is shown in Figure 3.

In addition, analysis of: PT, RT, drug effect on the NWR (latency, AUC), and cortical measures (latency, peak-to-peak amplitude) were performed between post-dose treatments by subtracting the baseline measure from the post-dose measure and comparing them. No differences were found (all $P > .05$).

3.1 | Inverse modelling

Four dipoles were selected to describe the brain activity adequately. The locations of the dipoles are shown in Figure 4. For dipole 1, the

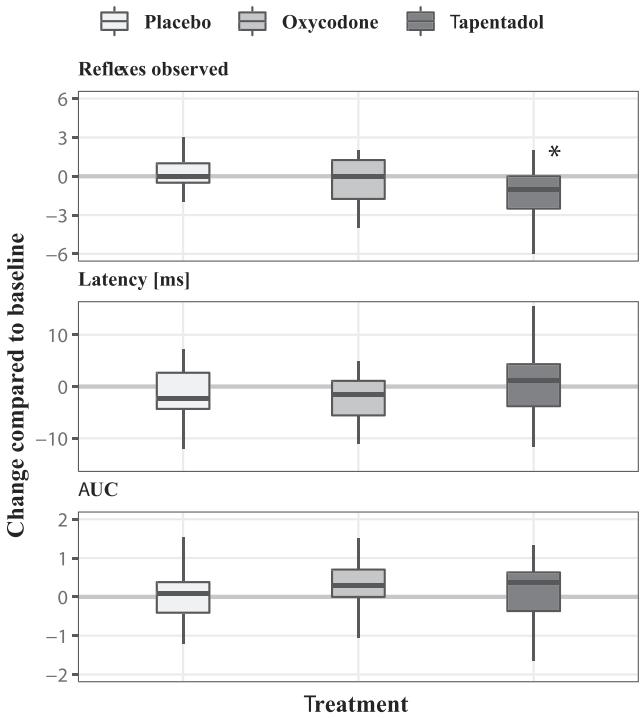

FIGURE 2 Boxplot of differences between the baseline and post-intervention of: Reflexes observed using the interval *z*-score, latency of the recorded nociceptive withdrawal reflex (NWR), and the difference in AUC of all the recorded NWR for each treatment. * Significant changes with $P < .05$

y-coordinate changed over time ($P < .001$). The post hoc test revealed the change to be across all treatment arms (placebo: $P = .012$, 95% CI −23.10, −2.10, oxycodone: $P < .001$, 95% CI −36.32, −15.24, tapentadol: $P = .001$, 95% CI −26.58, −5.48). In dipoles 2–3, the y-coordinates changed overall ($P = .001$), where the post hoc analysis did not reveal any differences between treatments. The z-coordinates differed over time ($P < .001$); the post hoc analysis showed a change of the oxycodone ($P = .022$, 95% CI −9.20, −0.51) and tapentadol ($P = .001$, 95% CI −10.88, −2.17) arms. The x-coordinate did not change over time. No coordinates changed over time for dipole 4. Data are presented in Table 1 and Figure 4. No differences in the residual variance were observed between baseline and post-intervention (all $P > .05$).

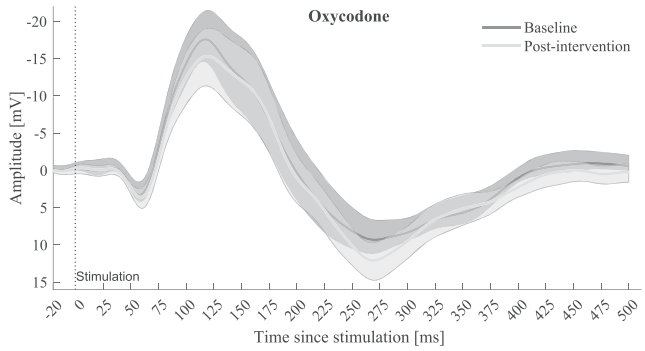

FIGURE 3 Average EEG evoked potential at the Cz electrode following electrical stimulation of the foot at baseline and post-intervention for the oxycodone treatment. The shaded areas of the graph are the corresponding 95% confidence intervals of the means

In addition, dipole locations were analysed between post-dose treatments by subtracting the baseline measure from the post-dose measure and comparing them. No differences were found (all $P > .05$).

4 | DISCUSSION

We explored the effects of oxycodone (μ receptor agonist) and tapentadol (μ receptor agonist and noradrenaline reuptake inhibitor) using

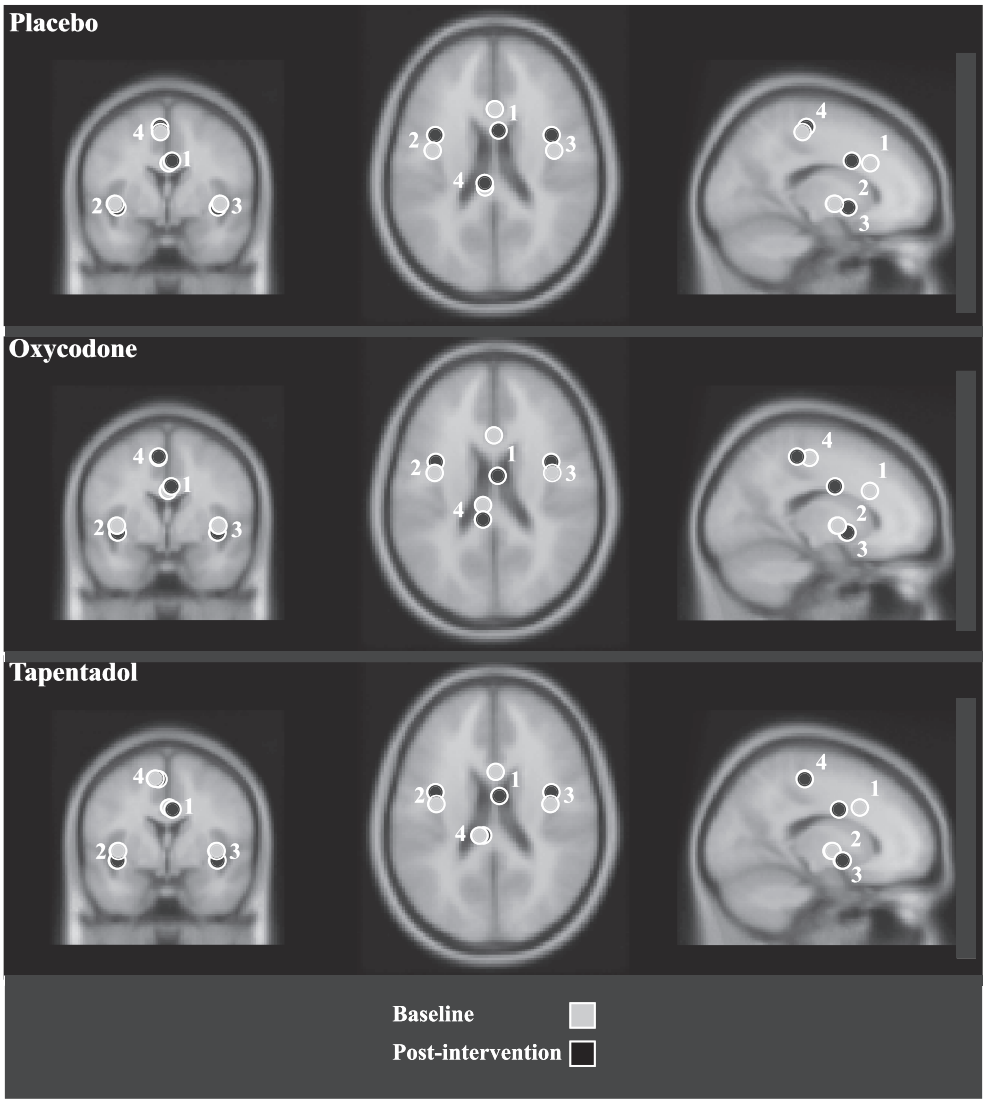

FIGURE 4 Average of the dipoles obtained using inverse modelling. The baseline is displayed in grey while the post-intervention is displayed in black. Dipole 1 is located in the anterior cingulate, dipoles 2 and 3 are mirrored and located in insula, and dipole 4 is in the midcingulate area

TABLE 1 Dipoles (1–4) represented in Talairach coordinates. Data are presented as mean ± standard deviation and 95% confidence interval of the mean. The result of the post hoc analysis is displayed when there was a main significant effect, all significant post hoc findings are marked in bold. All non-significant main effects had a *P*-value of >.09. The data for baseline (Bl) and post-intervention (I) are displayed. Dipole 1 is located in the anterior cingulate, dipoles 2 and 3 are mirrored and located in insula, and dipole 4 is in the midcingulate area

Location of inverse modelled dipoles				
Dipole 1				
Day		**Placebo**	**Oxycodone**	**Tapentadol**
Bl	*x*	1.76 ± 6.33; [−1.2, 4.72]	−0.07 ± 6.05; [−2.9, 2.76]	0.87 ± 4.76; [−1.3, 3.04]
I	*x*	2.33 ± 7.41; [−1.14, 5.80]	2.78 ± 6.74; [−0.38, 5.94]	2.96 ± 7.09; [−0.46, 6.38]
Bl	*y*	22.24 ± 12.77; [16.27, 28.21]	22.08 ± 13.23; [15.89, 28.27]	14.68 ± 15; [7.85, 21.51]
I	*y*	9.64 ± 22.77; [−1.02, 20.3]	−4.34 ± 13.52; [−10.67, 1.99]	−1.13 ± 17.21; [−9.43, 7.17]
	Post hoc	***P* = .012; [−23.1, −2.1]**	***P* < .001; [−36.32, −15.24]**	***P* = .001; [−26.58, −5.48]**
Bl	*z*	26.09 ± 11.34; [20.78, 31.4]	24.72 ± 6.51; [21.67, 27.77]	31.02 ± 9.03; [26.91, 35.13]
I	*z*	26.68 ± 6.81; [23.49, 29.87]	29.02 ± 5.52; [26.44, 31.6]	29.14 ± 7.5; [25.53, 32.75]
Dipole 2				
Bl	*x*	−39.58 ± 4.99; [−41.91, −37.25]	−38.85 ± 5.25; [−41.31, −36.39]	−37.16 ± 5.58; [−39.7, −34.62]
I	*x*	−37.79 ± 5.19; [−40.22, −35.36]	−37.82 ± 5.29; [−40.3, −35.34]	−37.7 ± 4.98; [−40.1, −35.3]
Bl	*y*	−6.25 ± 16.97; [−14.19, 1.69]	−4.04 ± 17.1; [−12.04, 3.96]	−6.8 ± 16.31; [−14.22, 0.62]
I	*y*	4.04 ± 14.9; [−2.93, 11.01]	3.23 ± 16.37; [−4.43, 10.89]	0.96 ± 15.61; [−6.56, 8.48]
	Post hoc	*P* = .078; [−0.79, 21.38]	*P* = .374; [−3.81, 18.41]	*P* = .247; [−3.05, 19.22]
Bl	*z*	−1.12 ± 6.3; [−4.07, 1.83]	0.88 ± 7.37; [−2.57, 4.33]	0.26 ± 6.76; [−2.82, 3.34]
I	*z*	−4.72 ± 5.25; [−7.18, −2.26]	−3.92 ± 5.54; [−6.51, −1.33]	−6.28 ± 4.46; [−8.43, −4.13]
	Post hoc	*P* = .142; [−7.94, 0.75]	***P* = .022; [−9.2, −0.51]**	***P* = .001; [−10.88, −2.17]**
Dipole 3				
Bl	*x*	39.58 ± 4.99; [37.25, 41.91]	38.85 ± 5.25; [36.39, 41.31]	37.16 ± 5.58; [34.62, 39.7]
I	*x*	37.79 ± 5.19; [35.36, 40.22]	37.82 ± 5.29; [35.34, 40.3]	37.7 ± 4.98; [35.3, 40.1]
Bl	*y*	−6.25 ± 16.97; [−14.19, 1.69]	−4.04 ± 17.10; [−12.04, 3.96]	−6.8 ± 16.31; [−14.22, 0.62]
I	*y*	4.04 ± 14.9; [−2.93, 11.01]	3.23 ± 16.37; [−4.43, 10.89]	0.96 ± 15.61; [−6.56, 8.48]
	Post hoc	*P* = .078; [−0.79, 21.38]	*P* = .374; [−3.81, 18.41]	*P* = .247; [−3.05, 19.22]
Bl	*z*	−1.12 ± 6.3; [−4.07, 1.83]	0.88 ± 7.37; [−2.57, 4.33]	0.26 ± 6.76; [−2.82, 3.34]
I	*z*	−4.72 ± 5.25; [−7.18, −2.26]	−3.92 ± 5.54; [−6.51, −1.33]	−6.28 ± 4.46; [−8.43, −4.13]
	Post hoc	*P* = .142; [−7.94, 0.75]	***P* = .022; [−9.2, −0.51]**	***P* = .001; [−10.88, −2.17]**
Dipole 4				
Bl	*x*	−5.71 ± 9.93; [−10.36, −1.06]	−6.92 ± 8.11; [−10.71, −3.13]	−9.55 ± 6.82; [−12.65, −6.45]
I	*x*	−5.74 ± 5.11; [−8.13, −3.35]	−7.16 ± 5.97; [−9.95, −4.37]	−6.12 ± 7.12; [−9.55, −2.69]
Bl	*y*	−26.98 ± 6.78; [−30.16, −23.8]	−21.91 ± 10.44; [−26.79, −17.03]	−26.34 ± 8.38; [−30.15, −22.53]
I	*y*	−24.34 ± 8.52; [−28.33, −20.35]	−31.77 ± 8.24; [−35.63, −27.91]	−26.09 ± 6.60; [−29.27, −22.91]
Bl	*z*	49.41 ± 5.61; [46.79, 52.03]	49.4 ± 12.29; [43.65, 55.15]	52.51 ± 4.84; [50.31, 54.71]
I	*z*	53.47 ± 4.80; [51.22, 55.72]	51.03 ± 6.20; [48.13, 53.93]	51.48 ± 5.79; [48.69, 54.27]

the NWR and the corresponding EMG and EEG signals. At the spinal level, tapentadol decreased the odds of eliciting an NWR. No other differences were demonstrated in EMG. At the cortical level, oxycodone increased the latency of the N1 component of the SEPs at the vertex. The inverse modelling revealed that the insula components changed during both oxycodone and tapentadol treatments. These findings suggests that oxycodone mainly affects cortical pain processing, whereas tapentadol modulates analgesia at the cortical and spinal levels.

4.1 | Sensory properties and electromyographic findings

Tapentadol treatment decreased the odds of eliciting the NWR. Tapentadol employs its analgesic in part with noradrenaline reuptake inhibition.[2] This has been shown in preclinical experiments to affect the brain stem's descending nerve tracts, which can inhibit the incoming nociceptive barrage at the spinal level.[32] Previous studies have shown that low doses of opioids did not affect the NWR.[9,33,34] Willer

found a linear increasing relationship between intravenous **morphine** administration and the related pain of the NWR.[32] In addition to this, Bossard et al. found that the nociceptive withdrawal reflex was reduced after a combination of morphine and **ketamine**, but not after individual administration of the drugs.[33] Lelic et al. investigated oxycodone and **venlafaxine** (a **serotonin** and **norepinephrine** reuptake inhibitor) and demonstrated that venlafaxine affected the NWR while oxycodone did not.[9] This could suggest that tapentadol's noradrenaline reuptake inhibitor mechanisms similarly affect the NWR. Lastly, an increased odds ratio of eliciting an NWR with increasing stimulus intensities was observed. This was expected, as higher stimulation intensities result in larger reflex amplitudes. Arguissain et al. found significantly larger amplitude reflexes when comparing above-threshold stimulations (1.5 × RT and 2 × RT) to lower stimulations (0.5 × RT and 0.75 × RT).[35] The analgesic effects of oxycodone and tapentadol were also tested in the current trial and they were found to decrease perceived pain by 7–11% in oxycodone and 6–9% in tapentadol after submerging the hand in cold water.[18]

4.2 | Cortical changes at the scalp

The only change observed in the SEPs was an increase in the latency of the N1 component in the oxycodone arm. This indicates altered responses of the later cortical signal, possibly due to decreased phase-locking of signals after administration of opioids.[36] The N1 component is in part driven by sources in the secondary somatosensory cortex, insula and the anterior cingulate cortex.[37] Generally, changes in SEP amplitudes correlate with clinical effect, while latencies of the SEPs are infrequently reported and with no coherent pattern.[38] The fact that there was no change in the tapentadol arm can also be attributed to the dual effect of tapentadol, where less μ-opioid receptor agonistic effect was needed for the same level of analgesia, and thus tapentadol does not affect the cortical signal to the same extent as oxycodone. These findings were collaborated in a study from the same trial which found changes in the processing of pain in oxycodone and tapentadol, but suggest that the oxycodone treatment has a larger cortical effect.[18]

4.3 | Inverse modelling

Four dipoles were chosen resulting in a residual variance of less than 10% in the baseline measures. The anterior cingulate cortex component of the inverse modelling moved caudally across all treatment arms, and the insula dipoles moved caudally in both the oxycodone and tapentadol arms. The anterior cingulate cortex and insula are involved in the processing of sensory stimuli, and while these networks do not only process pain-specific cortical processes, their magnitude has been shown to correlate with the magnitude of the perceived saliency of a stimulation.[39] The anterior cingulate cortex and insular cortex have been reported to play a role in previous pain studies.[9,40–42] The insula component only changed in the active treatments, suggesting a drug effect on the insula, probably due to the μ-opioid receptor agonist in both treatments. Previously, inverse modelling has also detected changes after opioid analgesia.[43] These findings are supported by another study from the same trial which found changes in functional connectivity in areas related to pain processing in oxycodone and tapentadol compared to placebo.[16] The dipole in the midcingulate area did not change in any treatment.

4.4 | Limitations

The experimental pain model was investigated in healthy young men without considering the differences in pain sensitivity and analgesic effect between men and women.[44–46] The rationale for selecting healthy young men was to test these complex experimental models in a homogeneous group. The choice to use a homogeneous group and a repeated measures design allowed the number of subjects to be relatively small; however, it does come with a risk of type 2 error. This contrasts a population with chronic pain and multiple comorbidities that often affect the reliability of the outcomes, and more subjects would be needed to investigate mechanistic effects.[47] Matthey et al. investigated milnacipran, a serotonin-norepinephrine reuptake inhibitor, on a fibromyalgia population using the NWR. They found that the milnacipran had a supraspinal analgesic effect, that did not change RT, but reported higher doses associated with higher pain reduction.[48]

Only minor changes were observed using EEG, which seems counterintuitive to several changes found using inverse modelling. Only one electrode at the vertex was analysed, which also corresponds with the only dipole in the inverse model that did not change location. The inverse modelling approximates the underlining cortical source generation and is not the only possible method to assess the effect of opioids on the central nervous system. Imaging methods, such as functional magnetic resonance imaging, have a higher spatial resolution. However, it does not have the temporal resolution of EEG and is less suitable for comparing spinal and supraspinal effects.[49] The observed changes could be related to drug effects such as analgesic effects but also side effects.

In conclusion, a decrease in the number of reflexes was observed only for the tapentadol treatment, on the spinal level. This could be due to the effects on the brainstem's noradrenaline reuptake inhibition. No other features of the NWR changed for any treatment. At the brain level, decreased latencies of the N1 component of the SEPs were identified only after the oxycodone intervention. Furthermore, the inverse modelling of dipolar sources in the insula component changed for both oxycodone and tapentadol treatments, indicating that both opioids affect cortical measures. This study replicates preclinical studies suggesting that the two opioids activate different pain control mechanisms and support clinical findings.

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COMPETING INTERESTS

There are no conflicts of interest to declare.

CONTRIBUTORS

A.M.D. and A.D. conceived the idea for the study. A.M.D., A.D. and M.N. designed the study. R.B.N. and T.M.H. conducted the study and wrote the manuscript. C.D.M. provided statistical advice. All authors participated in the interpretation of the study results and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author on reasonable request.

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