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Research Article

Aversion-related effects of kappa-opioid agonist U-50488 on neural activity and functional connectivity between amygdala, ventral tegmental area, prefrontal cortex, hippocampus, and nucleus accumbens

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Abstract

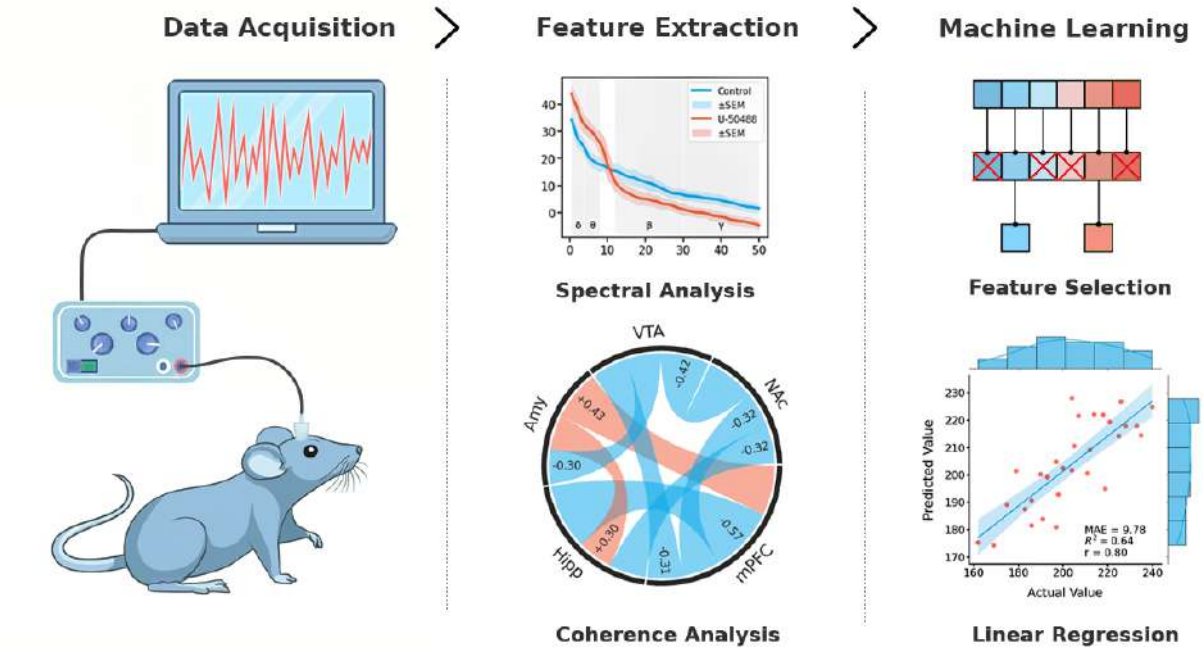
Introduction: Among the various receptor systems in the brain, the opioid receptors have been the subject of extensive research due to their integral role in pain modulation, reward processing, and emotional regulation. The kappa-opioid receptor (KOR) system, in particular, stands apart due to its unique contribution to stress response, aversive behaviors, and dysphoric states. This paper aims to provide an understanding of the neural activity underlying the aversion-associated effects of the KOR agonist U-50488.

Materials and Methods: Rats underwent stereotaxic surgery to implant electrodes into the amygdala, ventral tegmental area, prefrontal cortex, hippocampus, and nucleus accumbens. The rats were subjected to conditioned place preference test to measure aversion to U-50488. After that, local field potential (LFP) recordings were made. LFP data were processed and analyzed using spectral and coherence analysis methods. A stepwise multiple linear regression was employed to identify the LFP features most significantly correlated with aversion to U-50488.

Results: The administration of U-50488 resulted in significant changes in LFP signals across multiple brain regions. These changes were particularly notable in the theta, gamma, and delta bands of brain waves ($p<0.05$). Theta and gamma activities were especially sensitive to the effects of U-50488. Connectivity calculations revealed shifts in coherence between brain regions, particularly highlighting the amygdala's involvement. While changes were also observed in the ventral tegmental area, prefrontal cortex, hippocampus, and nucleus accumbens ($p<0.05$), they contributed less to aversion. Using the stepwise multiple linear regression method, we established a final model with the 3 most significant variables: (1) coherence between the amygdala and medial prefrontal cortex, (2) coherence between the amygdala and hippocampus, and (3) theta power in the amygdala.

Conclusion: Overall, the data provided insights into how electrical neural activity mediates aversion in response to KOR activation. The results showed that the severity of aversion can be reasonably predicted ($r=0.72\pm0.02$, $p=0.0099$) using LFP band power and functional connectivity data. We concluded that the amygdala is a brain region that contributes the most to the KOR agonist-induced aversion.

Graphical Abstract



Keywords

selective kappa-opioid agonist, U-50488, aversion, dysphoria, amygdala, LFP analysis, coherence, machine learning

Introduction

Kappa-opioid receptors (KORs) are one of the four main classes of opioid receptors in the brain, alongside mu (μ), delta (δ), and nociceptin (NOP) receptors. Historically, the focus of research on opioids has primarily been on the mu opioid receptors, largely due to their euphoric effects and role in pain management. The kappa opioid system and KOR agonists have gained significant attention due to their potential therapeutic applications and their distinctive aversive effects. The activation of KORs by selective agonists like U-50488 can produce anhedonia and stress-like responses (Page et al. 2019). The kappa opioid system is distinctive in its ability to mediate dysphoric, and anxiogenic effects, contrasting sharply with the euphoric responses typically associated with mu opioid activation (Khan et al. 2022). These aversive effects correlate with neural activity alterations in key brain regions implicated in emotional processing, reward, learning, and motivation. Central among these regions are the amygdala, ventral tegmental area (VTA), medial prefrontal cortex (mPFC), hippocampus, and the nucleus accumbens (NAc) (Liu et al. 2021; Lv et al. 2022; Salin et al. 2023).

While the full spectrum of U-50488's effects on brain function and neural circuits remains incompletely understood, insights that bridge this gap can be gleaned from local field potential analyses. The study of LFP (as well as ECoG and EEG) offers a direct window into the network-level oscillatory activity of neuronal populations and yields valuable information about inter-regional interactions (Bressler 2021; Sysoev et al. 2022a). Examining the effects of kappa-opioid agonists on LFP in specific brain areas can give an understanding of the underlying mechanisms by which KOR influences behavior and cognition (Kalitin et al. 2018).

Based on limited data, it is hypothesized that KOR activation, in particular by agonists like U-50488, can alter the synchronized activity or functional coupling between different brain regions (Coleman et al. 2021). There might be disrupted communication between the VTA and NAc, leading to reduced reward signals and hence the aversive effects. Enhanced connectivity between the amygdala and the prefrontal cortex can compromise top-down regulation of stress-related behavior and emotions.

Given the aforementioned context, the objective of this paper is to explore changes in LFP power and brain connectivity after kappa-opioid agonist administration. These changes can potentially serve as biomarkers of analgesic and aversive effects of novel compounds with kappa-opioid activity and provide critical insights into the pathways by which KOR agonists exert their effects. In

particular, this can help in the search for biased kappa-opioid agonists.

Materials and Methods

Experimental animals

Adult male Sprague Dawley rats (n=60), weighing 260–280 g were used in these studies. Animals were individually housed, maintained in a 12 h light/12 h dark cycle environment with controlled temperature (22±2°C), and provided food and water *ad libitum*. All procedures complied with the Principles of Good Laboratory Practice (State Standard of the Russian Federation GOST 33647-2015) and the Order of the Ministry of Health and Social Development of the Russian Federation dated 1 April, 2016 No. 199n "On Approval of the Rules of Laboratory Practice". Experiment protocols were approved by the Regional Research Ethics Committee of Volgograd Region (registration number IRB00005839 IORG0004900, Minutes No. 2022/096 of 21.01.2022).

Surgery

Rats under isoflurane anesthesia were positioned in a stereotaxic frame (SR-5R-HT; Narishige group, Japan). A single midline incision was made over the scalp and five holes, each with a diameter of 0.5 mm, were drilled through the skull for stereotaxic implantation of low impedance stainless steel electrodes (diameter = 0.1 mm). Stereotactic coordinates from bregma were: prelimbic cortex (PrL): anterior-posterior (AP) = +2.7 mm, medial-lateral (ML) = 0.8 mm, dorsal-ventral (DV) = 3.8 mm; basolateral amygdala (BLA): AP = –2.2–3.6 mm, ML = 5–5.3 mm, DV = 8.8 mm; hippocampus (Hipp): AP = –4.9 mm, ML = 4.8 mm, DV = 6.0 mm; ventral tegmental area (VTA): AP = –5.2 mm, ML = 1.0 mm, DV = 8.4–8.8 mm; nucleus accumbens (NAc): AP = +1.8 mm, ML = 1.6 mm, DV = 7.3 mm.

For the intracerebroventricular (i.c.v.) administration of drugs, a 21-gauge stainless steel guide cannula was implanted into the right lateral ventricle. Two stainless steel screws and dental polymer (Protacryl-M; Stoma, Ukraine) were used to secure the cannulas and electrodes to the skull surface.

LFP recordings

The experiments were conducted 5 days after surgery. LFP activity was recorded in a monopolar montage using a laboratory electroencephalograph NVX-36 (MCS, Russia). Signals were digitized at a sampling rate of 500 Hz. Following a 10-min baseline recording, animals underwent lateral i.c.v. injection with ACSF 5 µL (control group) and U-50488 (100 µg in 5 µL, Sigma-Aldrich, USA). Thirty minutes following compound administration, LFP activity was recorded for 10 minutes.

Conditioned place preference test

The conditioning apparatus (Open Science, Russia) consisted of three chambers. Two conditioning compartments (30x30x40 cm) were distinguishable by visual and tactile cues, and a smaller middle chamber (12x30x40 cm). The test consisted of three phases: pre-conditioning (one session), conditioning (six sessions), and post-conditioning (one session). All these sessions were conducted over 5 consecutive days (two conditioning sessions per day).

During the pre-conditioning phase (Day 1), the animals were placed into the CPP apparatus and were allowed free access to both conditioning chambers of the apparatus for 15 minutes.

During the conditioning phase (Days 2–4), the animals received i.c.v. injections of either ACSF (5 µL) or U-50488 (100 µg/rat) and were confined to one side of the CPP apparatus for 30 minutes. Four hours later, the rats were administered the alternate treatment and immediately confined to the opposite compartment for 30 minutes. In each group, 50% of the rats were initially placed in the preferred chamber, while the remaining 50% were placed in the non-preferred chamber.

On the final day (post-conditioning), the animals had unrestricted access to all compartments for 15 minutes. Preference change was quantified as the difference (in seconds) between the time spent in the U-50488-associated compartment on the post-conditioning day and the time spent in the same compartment on the pre-conditioning day.

The unpaired t-test was employed for comparing groups. Statistical significance was accepted at the level $p<0.05$.

LFP signal analysis

Processing the LFP data involved several stages including initial data cleaning, referencing, and the removal of muscle activity artifacts using independent component analysis (ICA). Subsequently, the LFP signals underwent bandpass filtering (0.5–50 Hz) with a linear finite impulse response (FIR) filter. Spectral analysis was performed by fast Fourier transformation (FFT) in Python. Frequency bands were defined as delta 0.5–4 Hz, theta 4–8 Hz, alpha 8–12 Hz, beta 12–30 Hz, and gamma 30–50 Hz.

The intra-hemispheric coherence between each pair of electrodes was analyzed in 1-second epochs. For each period, the magnitude squared coherence for each channel was calculated with the *mscohere* function (parameters: window = 1 s, noverlap, nfft = 500, fs = 500) built in MATLAB. The analysis of the data was performed only for the theta (4–8 Hz) frequency band. We chose the theta band of the spectrum for analysis based on the preliminary studies in which we observed the most pronounced changes within this frequency range. To normalize the data and conduct parametric statistical tests, we applied the Fisher z-transformation to all correlation coefficients.

The significance of differences among the groups was evaluated with unpaired t-test using GraphPad Prism 9.5. The criterion used to reject the null hypotheses was $p<0.05$.

Regression analysis

One data sample included 35 predictors (5 electrodes for power values × 5 frequency bands + 10 electrode pairs for coherence) and 1 dependent variable (directly observable behavior in the CPP test as a measure of aversion severity).

As the collected data included too many predictors and due to concern regarding over-fitting (severe deterioration of prediction accuracy when a model is applied to novel datasets) we employed a backward variable selection method. The stepwise multiple linear regression method was utilized for dimensionality reduction and identifying the most correlated LFP measures of aversion in rats. The stepwise multiple linear regression is a machine learning approach that iteratively removes predictors from the model based on the

significant/insignificant main effects on the regression model. In this model, the LFP power and coherence were the predictor variables and the aversion score (time difference obtained from CPP) was the response variable.

The five-fold cross-validation was repeated for 100 iterations. The resulting performance was calculated as the mean performance of all iterations and folds. To determine whether the observed correlation was significantly different from what might be expected by chance, we conducted a permutation test by permuting the aversion scores of rats 100 times. In each permutation, we randomly shuffled the aversion scores and then we repeated the cross-validation procedure explained above including all the steps of the training and testing. For each permutation, the mean absolute error (MAE) and the R^2 (coefficient of determination) values, averaged across folds, were obtained. Then, a permutation-based p-value was computed by dividing the number of times the shuffled value was greater than the true MAE value by 100 (the number of iterations).

Results

As depicted in Fig. 1A–E, the administration of U-50488 (100 µg/rat i.c.v.) produced complex changes in LFP

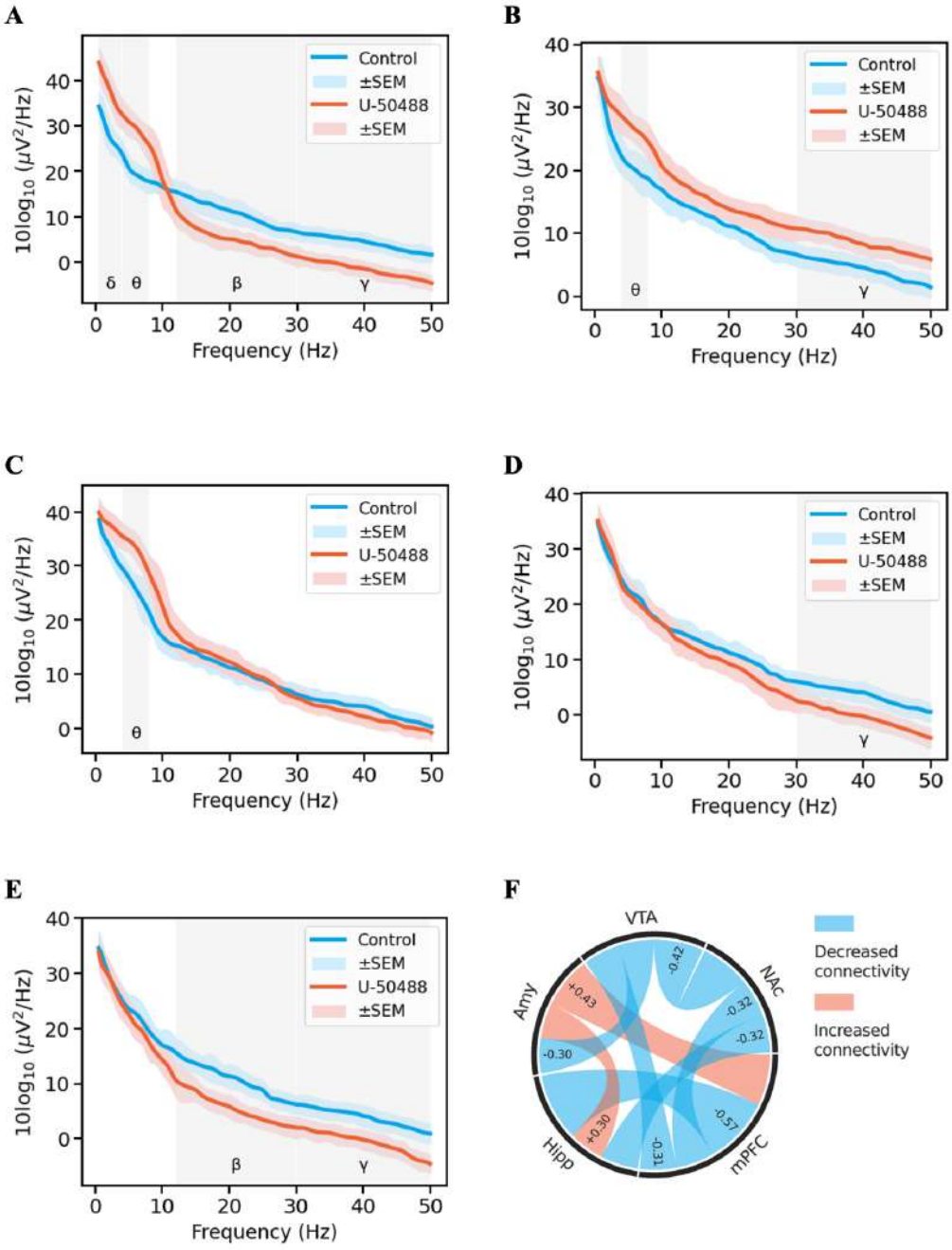


Figure 1. Power spectral density of LFP signals recorded from 30 to 40 min post-administration of U-50488 (100 µg/rat, i.c.v.) in the (**A**) medial prefrontal cortex (mPFC), (**B**) amygdala (Amy), (**C**) hippocampus (Hipp), (**D**) ventral tegmental area (VTA), and (**E**) nucleus accumbens (NAc), plotted as a function of frequency. Each graph presents the averaged power spectral density for both control and U-50488 groups. The solid traces depict the mean and the shading indicates ±SEM. Significant differences ($p<0.05$) are represented by gray shaded areas in each plot. (**F**) Chord diagram shows statistically significant changes ($p<0.05$) in LFP coherence from baseline in theta frequency range after U-50488 treatment. Red color represents increases and blue color indicates decreases in coherence.

signals recorded from all channels. Statistical analysis indicated that U-50488 significantly enhanced the power of theta band in the prefrontal cortex, amygdala, and nucleus accumbens between 30 and 40 minutes post-injection ($p<0.05$). The compound also increased delta power in the prefrontal cortex while it decreased gamma band power in the prefrontal cortex, amygdala, ventral tegmental area, and nucleus accumbens ($p<0.05$). Additionally, a decrease in the power of beta frequencies was observed in the signals recorded from the prefrontal cortex and nucleus accumbens ($p<0.05$). Among the brain waves, theta and gamma activity were found to be the most sensitive to U-50488 administration.

To delve deeper into the relationships between oscillatory LFP activity in the mPFC, Amy, Hipp, VTA, and NAc, network connectivity was calculated. The mean coherence changes in the 4–8 Hz band for combinations of brain recordings that are statistically different from the control group ($p<0.05$) are presented in Fig. 1F. In these 10 independent analyses, the results were consistent. There was a significant increase in coherence in six combinations, whereas a decrease was observed in only two connections, both of which involved the amygdala.

Administration of U-50488 resulted in a significant aversive response in the CPP test compared to the control group ($p<0.05$). Immediately after post-conditioning, we recorded LFP signals. A multiple linear regression model was constructed using the backward variable selection method to identify the most significant features of the LFP signals associated with aversion.

Based on the analysis, three variables were found to have the highest predictive power: (1) coherence between the amygdala and medial prefrontal cortex, (2) coherence between the amygdala and hippocampus, and (3) theta power in the amygdala. Notably, all three predictors were related to amygdala.

As can be seen in Fig. 2, the predicted values for aversion were in good agreement with the actual values. Here we applied 5-fold cross-validation to validate our results. Our findings reveal a positive significant correlation of $r = 0.72\pm0.02$, between the actual and the predicted values, with R-squared = 0.18 ± 0.08, MAE = 11.69 ± 0.08 with $p = 0.0099$ (Fig. 2A–B).

Discussion

Kappa-opioid receptors are widely distributed throughout the brain. Activation of KORs by U-50488 and other kappa-opioid agonists has been shown to produce aversive effects in animal models and humans, suggesting a role for KORs in the modulation of aversion. However, the precise neural mechanisms and functional interactions underlying these effects remain poorly understood.

The pharmaco-EEG approach enables the effective detection of antipsychotic, neuroprotective, and other psychotropic activities (Kalitin et al. 2022a; Sysoev et al. 2022b). In particular, we previously observed specific changes in rat electroencephalogram (EEG) following the administration of kappa-opioid agonists (butorphanol and RU-1205) during global cerebral ischemia (Kalitin et al. 2022b).

An EEG study in humans showed a significant increase in delta and gamma ranges and a decrease in alpha oscillatory activity when subjects were under the effect of kappa-opioid agonist salvinorin A (Ona et al. 2022). In another study, salvinorin A administration induced a reduction in beta-frequency spectral power range (13–29 Hz) at midline electrode sites in healthy humans (Ranganathan et al. 2012).

An increase in the power spectral density in the anterior region (in all frequency bands) and

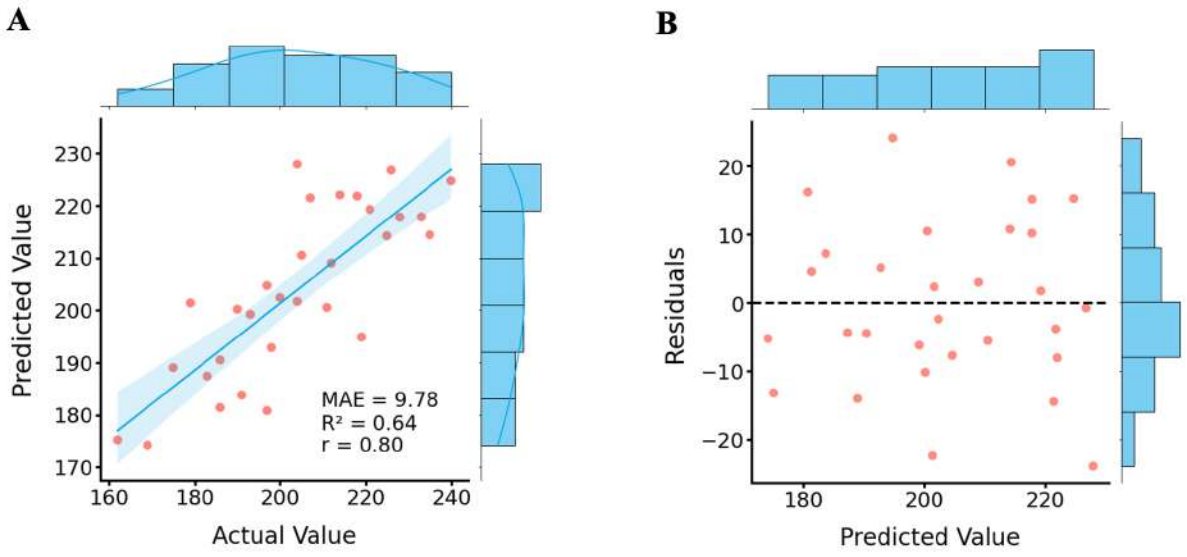


Figure 2. (**A**) Linear correlation plot between actual and predicted values of aversion for the whole dataset. Predictors selected for the multiple linear regression model: Amy-mPFC coherence, Amy-Hipp coherence and LFP theta power in Amy (all $p<0.05$). The right-hand margin histogram provides a depiction of the distribution of predicted values, while the top margin histogram illustrates the distribution of actual values. (**B**) Represents the graph of residuals vs. predicted values where the prediction made by the model is on the x-axis and the accuracy of that prediction is on the y-axis. The residuals are symmetrically distributed around zero. Histograms in the upper and right margins represent the distributions of predicted values and residuals.

an insignificant decrease in the posterior region were observed after the administration of Salvia divinorum extract in rats (Simón-Arceo et al. 2017).

In conscious rats, kappa-opioid agonists – in particular spiradoline, enadoline, BRL 52656, and BRL 53001 – were demonstrated to induce a decrease in EEG power within the theta band (4–7 Hz) (Coltro Campi and Clarke 1995).

Electrocorticographic (ECoG) effects of kappa opioids enadoline and PD117302 were studied in conscious, freely moving rats. Spectral analysis revealed a decrease in power in the 0–4 Hz band, coupled with an increase in the 4–8 Hz frequency range. The peak ECoG frequencies were 5.0 Hz and 4.8 Hz for enadoline and PD117302, respectively. There was also a significant shift in the mean EEG frequency from 6.6 Hz to 6.2 Hz after drug administration. Additionally, the drugs resulted in decreased edge frequency, mobility, and complexity of the EEG (Tortella et al. 1997).

Our data generally agree with prior findings. However, several issues regarding past research should be acknowledged: a) the majority of the referenced studies are dated; b) the existing research focuses solely on signals recorded from the cerebral cortex; c) direct effects of kappa-opioid agonists on functional connectivity are not documented; d) it remains undetermined which specific brain wave changes are related to aversive effects and which are associated with other effects, such as analgesic activity.

In Table 1, we provide data on LFP changes across various brain regions depending on aversive effects, including anhedonia, anxiety, depression, and sedation. The majority of the changes are nonspecific, and there are a substantial amount of conflicting results in the literature. Furthermore, the changes can vary based on the underlying cause of the aversive effect. At present, it remains unclear whether these changes will be induced by KOR agonists.

Table 1. Electrophysiological changes associated with aversive psycho-emotional states in various brain regions

Brain area	Anhedonia	Anxiety/fear	Depression	Sedation
Amygdala	Increased firing rate of central nucleus of the amygdala (Wang et al. 2016) Increased BLA cell firing <1 Hz (Reznikov et al. 2018)	Enhanced theta-gamma coupling (Stujenske et al. 2014)	Increased low theta waves and gamma frequencies (Merino et al. 2021) Faster firing of projection neurons in the stress-exposed group compared to controls (Neves and Grace 2019)	ND
VTA	VTA GABA neurons drive low frequency NAc LFP oscillations, rhythmically modulating NAc firing rates (Lowes et al. 2021) Decreased activity of VTA DA neurons (Markovic et al. 2021)	VTA DA cells baseline firing rate lowering (Corral-Frias et al. 2013; Guan et al. 2022)	Double or triple peaks at frequencies of 1–8 Hz and additional peaks at frequencies of 4–8 Hz (Friedman et al. 2012)	Reduced VTA GABA neuron firing rate and converted their activity into phasic 0.5–2.0 sec ON/OFF periods (Lee et al. 2001)
PFC	Reduced frequencies of spontaneous and miniature IPSCs Decreased release probability of perisomatic-targeting GABAergic synapses and alterations in $GABA_B$ receptor mediated signaling (Czéh et al. 2018)	Increases in both theta-frequency power in the mPFC and theta-frequency synchronization between the mPFC and ventral hippocampus (Sang et al. 2018)	Reduction in beta and gamma power (Jia et al. 2019)	Beta/low gamma (12–40 Hz) LFP power increased (Guidera et al. 2017)
Hippocampus	Decrease in spontaneous firing activity (Bambico et al. 2009) Reduction in theta energy and increase in gamma energy in the dentate gyrus region of the hippocampus. Attenuation of theta rhythm synchronization between perforant path and dentate gyrus and weakened theta-gamma cross-frequency coupling (Zhao et al. 2022)		Reduction in beta and gamma power (Jia et al. 2019) Increase in low theta and gamma frequencies (Merino et al. 2021)	Two spectral peaks, one in the theta range, the other at higher frequencies (25–50 Hz) (Soltesz and Deschênes 1993)
NAc	Reduced electrical excitability of NAcSh neurons (Wallace et al. 2009)	Increased LFP power in the theta frequency range (4–12 Hz) (Okonogi and Sasaki 2021)	Decrease in spontaneous firing rate (Crofton et al. 2017) Decreased magnitude of excitatory synaptic transmission (Wang et al. 2010) Decreased alpha, beta and low gamma LFP oscillatory activity (Voget et al. 2015)	Increase in EEG power of slow frequencies (4–6 Hz) (Slawecki 2002)

Note: basolateral amygdala (BLA); dopamine (DA); electroencephalogram (EEG); inhibitory postsynaptic currents (IPSCs); medial prefrontal cortex (mPFC); local field potential (LFP); nucleus accumbens shell (NAcSh); no data (ND); ventral tegmental area (VTA).

The use of deep electrodes greatly enhanced our understanding of the brain's electrical activity reorganization in response to compound U-50488. The changes we detected were consistent with the known side effects of kappa-opioid agonists. It should be noted that in this study both acute and chronic effects of U-50488 were observed, as the substance was administered regularly over a four-day conditioning period.

During our analysis we focused on quantifying aversion heterogeneity in terms of brain electrical activity and connectivity, rather than classifying data into binary categories. We avoided binary classification, as it offers limited insights into aversion heterogeneity and does not effectively test the potential continuum between severe and mild aversive states. Thus, we used the aversion levels obtained from the CPP to construct a predictive model based on LFP signal power. Furthermore, we integrated our analysis with connectome-based predictive modeling by taking into account the coherence data. The connectome-based predictive modeling is a recently developed method for identifying and modeling a brain network associated with a variable of interest, the aversion severity in our case (Ren et al. 2021). Connectome-based predictive modeling was previously employed in a number of studies to predict network alteration in several brain disorders such as anxiety related illnesses and sleep disorders as well in some other conditions such as creativity and personality traits (Kabbara et al. 2022).

We hypothesized that combining multiple LFP variables would predict aversion more accurately than a single variable, given the association of several brain regions and various frequency bands with aversion (Table 1). Using the backward variable selection method, we got a final model with the three most significant variables, all of which involved the amygdala. The findings align with previous data indicating the central role of the amygdala in mediating aversive reactions (O'Neill PK et al. 2018). The information obtained may be particularly useful in the study of biased kappa-opioid agonists.

Conclusions

In the study, the administration of U-50488 led to significant changes in LFP signals across multiple brain regions. These changes were particularly notable in the theta, gamma, and delta bands of brain waves. Among these, theta and gamma activities were especially sensitive to the effects of U-50488. Connectivity calculations revealed shifts in coherence between different brain regions, particularly highlighting the amygdala's involvement. While changes were also observed in the ventral tegmental area, prefrontal cortex, hippocampus, and nucleus accumbens, they were less significant in relation to aversion.

Using the stepwise multiple linear regression method, we established the final model with the 3 most significant variables linked to the amygdala, reaffirming its central role in aversive responses. It was suggested that combined metrics might predict aversion more accurately than single variables. Overall, the data revealed insights into how kappa-opioid receptors, which are found throughout the brain, influence aversion.

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Conflict of interests

The authors declare no conflict of interests.

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